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Adrenal Steroidogenesis and Congenital Adrenal Hyperplasia

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Synopsis

Adrenal steroidogenesis is a dynamic process, reliant on de novo synthesis from cholesterol, under the stimulation of ACTH and other regulators. The syntheses of mineralocorticoids, glucocorticoids and adrenal androgens occur in separate adrenal cortical zones, each expressing specific enzymes. Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive enzymatic defects in cortisol biosynthesis. 21-hydroxylase (21OHD) deficiency accounts for over 90% of CAH cases and when milder or nonclassic forms are included, 21OHD is one of the most common genetic diseases. This review discusses in detail the epidemiology, genetics, diagnostic, clinical aspects and management of 21OHD.

Keywords

steroidogenesis; congenital adrenal hyperplasia; 21-hydroxylase; androgen; steroid hydroxylase; adrenal insufficiency; ambiguous genitalia; disorder of sex development

I. Adrenal steroidogenesis

Adrenal steroidogenesis is a dynamic process, reliant on de novo synthesis, with no pre-synthesized hormones stored for immediate release. Cholesterol is the common precursor for all steroids and is efficiently converted along a series of steps to the final product. To initiate steroidogenesis, cholesterol is mobilized from a pool in the outer mitochondrial membrane (OMM)[1], which is replenished from cytosolic storage droplets of cholesterol esters. The steroidogenic acute regulatory (StAR) protein enables cholesterol transfer from the OMM to the inner mitochondrial membrane (IMM)[2], where the side-chain cleavage enzyme (CYP11A1, P450scc) catalyzes the first and rate-limiting step of steroidogenesis: the conversion of cholesterol to pregnenolone[1,3] (Figure 1A).

A. Aldosterone biosynthesis

Mineralocorticoid synthesis occurs in the zona glomerulosa (ZG), and requires the subsequent action of three enzymes: 1. 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), which performs the irreversible conversion of the hydroxyl group to a keto group on carbon 3 and simultaneous isomerization of the double bond from the Δ^5 to the Δ^4 position[4]; 2.21-

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hydroxylase (CYP21A2, P450c21), which converts progesterone into 11-deoxycosticosterone; 3. aldosterone synthase (CYP11B2, P450c11AS), which catalyzes the final three steps of aldosterone synthesis: 11β-hydroxylation, 18-hydroxylation, and 18-methyl oxidation. The 18-aldehyde group, from which the name "aldosterone" derives, forms an intramolecular cyclic hemiacetal using the 11β-hydroxyl group, with loss of water.

The ZG is optimized for aldosterone synthesis: it is the only zone that has CYP11B2 and, in contrast, has little 17α-hydroxylase/17,20-lyase (CYP17A1, P450c17), an enzyme which directs steroids substrates towards cortisol and androgens synthesis[5] (Figure 1B). Angiotensin 2 and high extracellular potassium are the main stimulators of aldosterone synthesis, via increased intracellular calcium[6].

B. Cortisol biosynthesis

The glucocorticoid cortisol is synthesized in the zona fasciculata (ZF) under the regulation of adrenocorticotropin (ACTH). CYP17A1 catalyzes the 17α-hydroxylation of pregnenolone and progesterone with roughly equal efficiency, and this reaction leads to cortisol production. In addition, CYP17A1 subsequently cleaves the C17-C20 bond of 17-hydroxypregnenolone and to a much lesser degree of 17-hydroxyprogesterone (17OHP), which leads to 19-carbon (C_{19}) steroids (Figure 1A). Both reactions occur in a single active site, but with different regulation, as described below. With the activities of HDS3B2 and CYP21A2, which perform reactions similar to those on the mineralocorticoid pathway, 17-hydroxysteroids are converted to 11-deoxycortisol. Lastly, 11β-hydroxylase (CYP11B1, P450c11β), an enzyme closely related to CYP11B2, completes the synthesis of cortisol. In rodents and many small animals, the ZF lacks CYP17A1. Consequently, nascent progesterone is 21- and 11β-hydroxylated to yield corticosterone, which is the dominant glucocorticoid in these species, but it is ordinarily a minor product of the human adrenal.

C. Adrenal androgen biosynthesis

Adrenal C_{19} steroids are synthesized in the zona reticularis (ZR). Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are the two most abundant adrenal steroids. CYP17A1 is the only enzyme required for DHEA synthesis from pregnenolone and for androstenedione (AD) synthesis from progesterone. While CYP17A1 is present in both ZF and ZR, its 17,20-lyase reaction is enhanced approximately 10 times by the cofactor cytochrome b_5 (CYB5A), which is absent in the ZF[7] (Figure 1B). Sulfotransferase SULT2A1 conjugates DHEA to DHEAS, a steroid with an important role in the regulation of adrenal androgen synthesis[8]. The adrenal synthesizes small amounts of testosterone, by the action of 17β-hydroxysteroid dehydrogenase type 5 (17βHSD5, AKR1C3) on AD (Figure 1A).

ACTH is the primary stimulus of steroidogenesis in the ZR and is required for ZR development[9,10]. Additional growth factors have been postulated to regulate adrenal androgen synthesis and to control the development of the ZR, but these remain poorly understood. The ZR resembles the fetal adrenal, which provides the C_{19} substrate for estrogen synthesis during pregnancy but involutes at birth. The ZR is only few cells thick at birth but expands during childhood, leading to a rise in circulating DHEAS and the phenomenon of adrenarche, which manifests as the development of axillary and pubic hair.

ZR function and serum DHEAS peak about age 25 and then gradually decline, falling to childhood values in the seventh or eighth decade of life.

II. Congenital adrenal hyperplasia

A. Definition and classification

Congenital adrenal hyperplasia (CAH) refers to a group of inherited enzymatic defects in cortisol biosynthesis. Impaired cortisol production relieves negative feedback to the hypothalamus and the pituitary gland, which in response amplify the secretion of corticotropin-releasing hormone (CRH) and ACTH, respectively, resulting in hyperplasia of the adrenal cortex. The spectrum of enzymatic deficiencies ranges from mild to complete and from a single activity to several activities. Steroid 21-hydroxylase deficiency (21OHD) accounts for over 90% of CAH cases[11]. Conventionally, 21OHD is dichotomized into classic and nonclassic forms, based on the presence or absence of cortisol insufficiency. The classic forms of 21OHD are further grouped into “salt wasting” and “simple virilizing” subtypes, depending on whether or not mineralocorticoid synthesis is sufficiently impaired to cause spontaneous hypotensive crises in the infant.

Other forms of CAH are summarized in Table 1. For additional information, the reader is directed towards recent reviews and chapters on deficiencies in CYP17A1[12], CYP11B1[13], HSD3B2[14], lipoid CAH[15], cholesterol side-cleavage enzyme (P450scc)[16] and P450-oxidoreductase (POR)[17]. This review will further expand the discussion of 21OHD.

B. Epidemiology

Classic 21OHD occurs in 1 of 16,000 live births worldwide[18]. Nonclassic 21OHD is much more frequent, occurring in approximately 1 of 1,000 Caucasians and more commonly in certain ethnic groups, such as Ashkenazi Jews (1:27), Hispanics (1:53), Yugoslavs (1:62) and Italians (1:300)[19]. The reason why classic 21OHD has a similar prevalence throughout most of the world is related to the structure of the RCCX locus containing the RP protein kinase, C4, CYP21, and tenascin X genes, including the *CYP21A2* gene encoding the CYP21A2 enzyme.

C. Genetics

All forms of CAH are inherited in a monogenic, autosomal-recessive pattern. Human 21-hydroxylase is encoded by *CYP21A2* gene, on chromosome 6p21.3, within the HLA major histocompatibility complex and adjacent to the genes for the fourth component of complement[20-22]. Only 30 kb away resides the non-functional *CYP21A1P* pseudogene, which encodes a truncated, inactive enzyme. Both *CYP21A2* and *CYP21A1P* contain 10 exons, and the 2 genes share 98% homology. The majority of mutant 21OHD alleles result from intergenic recombinations and gene conversion events between the two CYP21A genes[23]. Complete deletions, large gene conversions, and non-sense or frame-shift mutations that completely ablate 21-hydroxylase activity typically result in salt-wasting forms of CAH. Mutations resulting in even 1-2% residual enzyme activity allow sufficient aldosterone production and lead to simple virilizing forms of CAH. Nonclassic 21OHD patients retain 20-60% of the enzyme activity and do not have adrenal insufficiency. Nonclassic 21OHD

patients may be either compound heterozygotes (with one classic allele and one nonclassic allele) or heterozygotes with two nonclassic alleles. While the most severe and mildest forms of the disease tend to maintain some genotype-phenotype correlation, the intermediate forms are often poorly linked with specific gene defects, suggesting other contributors (genetic or environmental) to the phenotypical expression[23].

D. Biochemistry of 21OHD

As a result of 21-hydroxylase dysfunction, upstream steroid precursors accumulate and are diverted towards accessible pathways to form potent androgens (Figure 2). Elevations of 17OHP, the main substrate of CYP21A2, are a hallmark of 21OHD, and 17OHP has traditionally been used for both diagnosis and monitoring of the disease. Additionally, the CYP21A2 blockage promotes the build-up of other C_{21} steroids. Human CYP17A1 hydroxylates pregnenolone and progesterone in position 17 with equal efficiencies, but also 16α-hydroxylates up to 30% of progesterone[24]. In the normal pathways to aldosterone and cortisol, progesterone and 17OHP are first hydroxylated at position 21 by CYP21A2, and subsequently at other positions. In 21OHD, progesterone and 17OHP accumulate and are substrates for CYP11B1, leading to 11β-hydroxyprogesterone (11OHP) and 21-deoxycortisol (21dF), respectively.

The excess 17OHP resulting from CYP21A2 deficiency is diverted through the pathways left accessible, to form potent androgens, such as testosterone and 5α-dihydrotestosterone (DHT). CYP17A1 mediates the conversion of 17-hydroxypregnenolone to DHEA (Δ^5 pathway) and of 17OHP to AD (Δ^4 pathway). The catalytic efficiency of the human 17,20-lyase, however, is approximately 100 times greater for the Δ^5 reaction, as compared with the Δ^4 reaction[25], explaining the enormous 17OHP accumulation in 21OHD. In patients with 21OHD, significant AD synthesis might still occur via the Δ^4 pathway due to very high intra-adrenal 17OHP.

More recently, a third potential fate of 17OHP has been suggested in patients with 21OHD: androgen synthesis via the “backdoor pathway” (Figure 2). This pathway was initially described a decade ago in tammar wallabies, whose testes produce 5α-androstane-3α,17β-diol (5αAdiol) rather than testosterone[26]. The 17OHP is first 5α-, then 3α-reduced, and only subsequently undergoes 17,20-lyase cleavage, to form androsterone. After 17β-reduction to 5αAdiol, circulating 5αAdiol is 3α-oxidized to produce DHT in target tissues such as genital skin and prostate, thus bypassing the conventional androgens AD and testosterone as intermediates. This pathway might contribute to the virilization of female fetuses with CAH[27]. Kamrath and colleagues were the first to demonstrate increased excretion of 5α-reduced products and intermediates of the backdoor pathway in 142 patients with CAH between 1 and 25 years old, compared to 138 similarly aged controls[28]. Using gas chromatography/mass spectrometry (GC/MS), they found significantly increased urinary excretion of 5α-pregnane-3α,17α-diol-20-one (Pdiol), the critical intermediate and a specific marker of the backdoor pathway, in patients with 21OHD. Furthermore, they reported 7-fold elevations of urinary androsterone, the dominant 5α-reduced C_{19} steroid derived from both classical and backdoor pathways, in children and young adults with 21OHD. In contrast, they found only a 2-fold elevation in etiocholanolone, the 5β-reduced

C_{19} derived only from the classical pathways. Importantly, 5α-/5β-reduced cortisol metabolites ratios were not different in controls and 21OHD, excluding a general increase in 5α-reductase activity to explain their data[28].

E. Diagnosis

Diagnosis of 21OHD relies on elevated 17OHP, one of the direct substrates of the deficient enzyme. The 17OHP levels are reflective of disease severity. Most patients with classic 21OHD have 17OHP levels consistently above 10,000 ng/dL, while unaffected patients typically have baseline 17OHP values below 200 ng/dL[29]. In nonclassic 21OHD, a random 17OHP is often equivocal, and post-cosyntropin values >1,200 ng/dL are required to make the diagnosis. A few nonclassic 21OHD patients who are compound heterozygotes for classic and nonclassic alleles will have stimulated 17OHP values >10,000 ng/dL, but by definition, they lack clinically significant adrenal insufficiency, with stimulated cortisol values >14 μg/dL.

E.1. Newborn screening—Screening of newborns for CAH is performed in all 50 of the United States. Screening decreases the time to diagnosis and improves morbidity and mortality[30-33], particularly by preventing salt wasting crises. Males with CAH are more likely to not be diagnosed early clinically, as they do not exhibit genital ambiguity at birth.

First-tier screening utilizes dried blood spots on standard screening cards and measures 17OHP by immunofluorometric assay (DELFIA®). A very high random 17OHP (>20,000 ng/dL) is diagnostic of 21OHD. False-positive results, however, are common in premature and severely ill infants[34,35]. Thus, weight and gestational age adjusted cutoffs for 17OHP improve the positive predictive value of screening[36-38]. False negative rates of up to 22% have been reported in infant screening[39,40], particularly when mothers had been exposed to glucocorticoids prenatally. Although false negative results are reportedly more common in girls[40], it is possible that missed males remained unidentified, while the diagnosis was more likely to be pursued in girls, who are born with ambiguous genitalia.

Some of the limitations of immunoassay-based screening can be overcome by adjudicating positive tests with a second-tier assay using liquid chromatography/tandem mass spectrometry (LC-MS/MS)[41-43]. In addition to increased specificity, LC-MS/MS can also quantify multiple steroids with one measurement. Elevated 21dF by LC-MS/MS has been shown to increase the sensitivity of newborn screening[42] and better discriminate heterozygote carriers[44]. LC-MS/MS assays, however, are not widely available, are often time-consuming, and are prohibitively expensive for screening purposes currently.

E.2. Diagnosis of 21OHD beyond infancy—Patients evaluated for clinical evidence of inappropriate androgen excess initially undergo testing of 17OHP in an early morning serum sample[29]. The gold standard for diagnosing any form of CAH in patients with indeterminate values is a cosyntropin stimulation test, which maximizes the ratio between the steroids upstream and downstream the enzymatic blockage[45]. Figure 3 shows suggested cutoff baseline and stimulated 17OHP values in patients with 21OHD. Genetic testing of *CYP21A2* detects 90 to 95% of mutant alleles[46] and is useful when steroid results are equivocal[47] or unreliable (hypopituitarism) and for genetic counseling, particularly in nonclassic 21OHD.

Because other forms of CAH are not tested, the cost is high and management is rarely changed, genetic testing is not routinely recommended.

F. Clinical Features

Salt wasting—Approximately three-quarters of patients with classic 21OHD have aldosterone deficiency and thus are prone to volume depletion and hyperkalemia[48]. Where neonatal screening is not performed, undiagnosed male infants might present with failure to thrive and dehydration in the first 2 weeks of life, which can lead to death if not appropriately recognized and treated. All untreated classic 21OHD patients waste salt during illness, but spontaneous volume depletion in a well infant defines “salt-wasting” disease, a term that has little utility beyond childhood.

Ambiguous genitalia and prenatal virilization—Girls with classic 21OHD of all severities are born with varying degrees of genital ambiguity. Prenatal exposure to adrenal androgens activates the androgen receptors in genital skin, favors clitoral enlargement and labial fusion, and interferes with the urogenital sinus septation, which normally occurs at 7 weeks of gestation in girls. The degree of virilization is classified according to the 5-point Prader scale (Figure 4). If virilization is severe (Prader 4-5), assignment to male sex of rearing might inadvertently occur, and in rare cases, parents choose to raise the child as a boy knowing the diagnosis.

Boys with classic 21OHD typically have normal male genitalia (Prader 5). Subtle findings, such as hyperpigmentation of the scrotum and enlarged phallus, might be present at birth.

Postanatal virilization—In inadequately treated classic 21OHD, the adrenal androgen excess promotes further clitoral growth in girls and phallus enlargement in boys. Children with nonclassic 21OHD may exhibit evidence of androgen excess at various ages, such as premature pubarche and oily skin, but not genital virilization. Poorly controlled adolescent girls might experience hirsutism, acne, and irregular menses, similarly with polycystic ovarian syndrome patients[48].

Growth—Both male and female infants with classic 21OHD are longer than average at birth[49]. Increased circulating levels of sex steroids promote accelerated linear growth and bone maturation early in life, which results in below average final height, due to premature epiphiseal closure. Additionally, glucocorticoid treatment, especially when excessive, suppresses growth. A meta-analysis of data from 35 centers concluded that the near-final height of patients with classic 21OHD was -1.38 SD below the population mean and -1 SD below the predicted mid-parental height[50]. A multitude of factors influence adult height, including severity of disease[51], age at diagnosis[49], treatment regimen[52,53] and compliance. These known factors, however, failed to prove significant individually in pooled data, possibly because of heterogeneity and inconsistent reporting between studies. Both boys and girls can experience central precocious puberty when control is poor or erratic, thought to be due to adrenal-derived sex steroid “priming” and withdrawal, which further compromises adult height.

Psychosexual development—Girls with classic 21OHD show more male-pattern play, activities, and career preferences[54,55]. Additionally, some studies have found that affected girls display more aggressive behaviors and lower maternal drive as compared with their unaffected siblings[56,57]. Exposure to higher than normal androgens prenatally and in childhood is thought to "imprint" the brain, leading to masculine behavior but rarely to male gender identity if treated from birth.

Some studies suggest that females with 21OHD, particularly those with more severe forms, undergo male-like cognitive development, with higher visuospatial and logic performance and lower verbal abilities[58-60]. Data regarding the overall intelligence coefficient (IQ) of patients with 21OHD have been conflicting. It has been suggested that salt-wasting 21OHD might result in lower IQs, possibly due to electrolyte imbalances in infancy[61]. Conversely, other authors found no overall IQ or cross-gender performance differences between 21OHD patients and unaffected controls[62].

Female reproduction—Women with 21OHD have lower fertility rates, which correlate inversely with disease severity[63,64]. The live-birth rates in salt-wasting classic 21OHD have been reported to be only up to 10%, 33-50% in simple virilizing forms, and 63-90% in nonclassic 21OHD, the latter rate being similar to that observed in the general population[65-69]. Hormonal, anatomical, and psychosocial factors have been suggested to contribute to impaired fertility[64]. Adrenal androgen overproduction can inhibit ovarian folliculogenesis and disturb the normal gonadotropin secretion pattern[69,70]. Elevated adrenal-derived progesterone in the follicular phase interferes with the normal menstrual cycle and impairs sperm penetration[66,71,72]. Women with 21OHD may also have excessive ovarian androgen production[73,74] and secondary PCOS[75].

Non-hormonal contributors to decreased fertility in 21OHD women include distorted genital anatomy, such as vaginal stenosis and reduced clitoral sensitivity, as well as decreased sexual motivation[67,76] and lower maternal interest[54]. Nevertheless, in women with classic 21OHD who attempt pregnancy under skilled management, fecundity rates are normal[77].

In contrast to the frequent development of adrenal rest tumors in the testes of men with 21OHD, ovarian adrenal rest tumors have only sporadically been reported in affected women[78-81]. This difference could be due to several factors, including more difficult distinction of ectopic adrenal tissue from theca cells in the heterogeneous ovary, the position of the ovaries in the pelvis, and possibly better control in most women, in whom undesirable clinical manifestations of androgen excess might provide motivation for compliance.

Male reproduction—Fertility in men with 21OHD has not been studied as extensively as in women. In the absence of newborn screening, boys with simple-virilizing 21OHD might remain undiagnosed, until they present with sexual precocity, accelerated growth, adrenal crisis during an infection, or rarely after fathering an affected girl. Studies from UK and Finland suggest that male fertility is well below that of the normal population[82,83]. The two main contributors to male infertility in 21OHD are hypogonadotropic hypogonadism, due to gonadal axis suppression from adrenal-derived androgens, and testicular adrenal rest tumors (TARTs)[84,85].

TARTs are typically bilateral masses, arising in the rete testes, thus often non-palpable when small[84]. Ultrasound studies have identified TARTs in over 20% of boys[86,87] and up to 94% of adults with classic 21OHD[84,85,88]. Some, but not all TARTs, regress following intensified glucocorticoid treatment[89]. The variable response might be in part due to fibrotic changes[90] and to the number of adrenal-lineage cells, which migrated to the gonad during embryologic development[91]. TARTs may lead to obstruction of seminiferous tubules, gonadal dysfunction, and infertility[84]. Surgery to remove TARTs give good long-term control of tumor growth and mass effect[92,93], but rarely restores fertility or testicular testosterone production[93,94]. For this reason, medical therapy is continued as primary treatment as long as the luteinizing hormone (LH) is in the normal range, the rests are shrinking, and the testosterone is rising, for at least 6 months and longer if tolerated. A rise in follicle-stimulating hormone (FSH) and fall in inhibin B indicate loss of Sertoli cell function and poor prognosis for restoration of testicular function. Abrupt resumption of tight disease control in patients with TARTs and suppressed testicular function will lower serum testosterone into the hypogonadal range. To enhance compliance, the patient should be warned of these changes, and a gradual increase in medication should be considered. TARTs rarely if ever occur in men with nonclassic 21OHD. Little is known about fertility in men with nonclassic 21OHD, as few are ever diagnosed, and men with unexplained infertility are rarely tested for 21OHD.

Adrenal masses—A high prevalence of benign adrenal masses has been reported in patients with 21OHD. Over 80% of homozygous and 45% of heterozygous patients had adrenal tumors in one study[95], although no correlation between tumor size and serum 17OHP concentrations was found. Most tumors had a diameter of less than 2 cm, but several giant myelolipomas have also been reported, typically in patients who are chronically under-treated[96-98].

Metabolic abnormalities—In a prospective cross-sectional study which followed 203 patients with CAH, 41% were obese, 46% had hypercholesterolemia, 29% were insulin-resistant, 40% had osteopenia, and 7% had osteoporosis[82]. Similar findings have been reported in smaller studies[99-101] and have been mostly attributed to glucocorticoid overtreatment.

G. Management

G.1. Medical treatment—Glucocorticoids and mineralocorticoids are the mainstays of treatment for 21OHD. Glucocorticoids exert two principal actions: replacement of the deficient cortisol and suppression of the adrenal androgen overproduction, by exerting negative feedback on the hypothalamus and the pituitary, which subsequently decreases CRH production and ACTH stimulation.

G.1.a. Glucocorticoid replacement: Patients with classic 21OHD all require chronic glucocorticoid replacement. Hydrocortisone is preferred in children and adolescents, until growth is completed, due to its short action, which limits the potential to suppress growth. A total of 10-17 mg/m^2 daily divided in 2-3 doses is typically recommnended[29], although it remains unclear if a specific dose distribution throughout the day has a significant clinical

impact[102]. The lowest possible dose should be used in order to avoid growth suppression[51,53,103,104].

Hydrocortisone also serves as replacement therapy for adults, but long-acting synthetic glucocorticoids are often preferred, owing to less frequent dosing. The longer duration of action and higher potency of drugs like prednisolone and dexamethasone, however, might increase the risk of detrimental effects, including weight gain, dermal atrophy, poor sleep, and bone loss[82,105-108].

Available treatment options and suggested doses are shown in Table 2. Stress doses of steroids should be given in patients with classic 21OHD during surgery, physical illness, labor and delivery[29]. In women attempting to conceive and during pregnancy, a glucocorticoid that is inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 (e.g., hydrocortisone, prednisone, and prednisolone) should be used, to avoid fetal exposure.

Asymptomatic patients with nonclassic 21OHD do not require treatment, and stress doses of steroids are rarely needed. Glucocorticoid treatment is primarily given to children with sexual precocity and advanced bone age or to women with infertility due to this condition. For other consequences of androgen excess, including acne, hirsutism, or body odor, alternatives therapies include anti-androgens (spironolactone), oral contraceptives, and mechanical depilation. When treated, replacement regimens are similar to those prescribed to classic 21OHD patients with lower doses. One retrospective series found high rates of pregnancy loss in women with nonclassic 21OHD, but this rate was lower in women who were treated with glucocorticoids[109]. For this reason, glucocorticoids (hydrocortisone) are often continued throughout gestation, particularly in women who conceive while taking glucocorticoids.

The goals of therapy for classic 21OHD are to replace the hormonal deficits, while adequately suppressing the androgen excess. This balance is often hard to achieve without causing iatrogenic Cushing syndrome. Near-normalization of AD in both men and women and of testosterone in women indicates adequate control in most circumstances. Conversely, the 17OHP should not be consistently in the normal range; values of 1,000-3,000 ng/dL are acceptable if androgens production is controlled[110]. An exception is women attempting pregnancy, in whom treatment needs to be intensified to keep the follicular-phase progesterone suppressed (<0.6 ng/mL). Men with TARTs require at least one dose of a long-acting glucocorticoid to keep the ACTH suppressed and to allow regression.

G.1. b. Mineralocorticoid replacement: Mineralocorticoid replacement (fludrocortisone acetate, 0.1-0.3 mg daily) is necessary in patients with classic 21OHD. Infants with the most severe (salt-wasting) forms of disease need higher mineralocorticoid doses and additionally require supplementation with sodium chloride (1–2 g sodium chloride daily) while the renal function matures[111]. Mineralocorticoid replacement is generally maintained but occasionally becomes unnecessary in adults, possibly due to extra-adrenal 21-hydroxylation of adrenal-derived progesterone[112,113]. Mineralocorticoid replacement and restoration of euvolemia decreases vasopressin and ACTH secretion, which often lowers the dose of glucocorticoid required to achieve adequate control of androgen production[50,103]. The dose of

fludrocortisone is titrated to achieve normal sitting and standing blood pressure without an orthostatic drop, plasma renin activity near the lower limit of the normal range, and normal serum potassium; reevaluations should occur periodically.

G.1.c. Experimental therapy: Addition of the antiandrogen flutamide and the aromatase inhibitor testolactone allowed the use of lower doses of hydrocortisone and fludrocortisone acetate and normalized linear growth and bone maturation in children followed for 2 years[114,115]. Growth hormone, with or without a GnRH agonist, improved final height in some studies[116,117]. Additionally, GnRH antagonist has been successful in improving height in children with 21OHD and precocious puberty[117]. Abiraterone acetate, a potent CYP17A1 inhibitor indicated for testosterone suppression in patients with prostate cancer, when added to physiologic doses of hydrocortisone and fludrocortisone acetate, normalizes AD in adult women with classic 21OHD and elevated androgens[118]. Extended-release hydrocortisone preparations, which might improve compliance and limit the need for more potent glucocorticoids, are being studied[119]. Long-term safety data on all of these agents are lacking, and large, randomized controlled studies are yet needed.

G.2. Surgical treatment

G.2.a. Reconstructive surgery: For girls with virilized genitalia, surgery has been used to normalize voiding and to enable vaginal intercourse, but no good evidence to support a specific timing for surgical correction exists. A multidisciplinary team gathering expertise from pediatric endocrinologists, surgeons, social workers and psychologists should support the family into making an individualized decision. Advantages of early surgery include tissue malleability[120] and decreased psychological impact on both affected girls and parents[63,121]. A potential benefit of delaying surgery until adolescence or young adulthood is incorporating patient autonomy in the decision-making process.

A two-step neurovascular-sparing clitoroplasty and vaginoplasty using total or partial urogenital mobilization is the preferred surgical approach, for minimizing clitoral insensitivity and urinary incontinence[29,122]. Good long-term outcomes data are difficult to obtain, due to the variations in surgical approach, baseline anatomy, hormonal control, and other mitigating factors. Post-surgical complications such as urethra-vaginal fistulae, impaired sensation, and vaginal stenosis, have been described, and current procedures strive to minimize these complications. The evolution of urogenital function following these procedures is particularly critical for young women contemplating pregnancy.

G.2.b. Elective adrenalectomy: Bilateral adrenalectomy has been performed in selected patients with severe forms of 21OHD, in whom hyperandrogenism was difficult to control despite generous glucocorticoid replacement or in order to avoid their associated side effects[123-125]. The ensuing primary adrenal insufficiency, however, is more tenuous than 21OHD and mandates strict adherence to lifelong glucocorticoid and mineralocorticoid replacement, in order to prevent potentially fatal adrenal crises[125,126]. Complete absence of epinephrine and DHEA are additional theoretical concerns, but the consequences of these deficiencies remain unknown.

G.3. Prenatal diagnosis and treatment—The goal of prenatal treatment is to prevent virilization of external genitalia in female fetuses with classic 21OHD. Administration of a glucocorticoid that is not degraded by the placenta, such as dexamethasone, suppresses fetal ACTH and the adrenal hyperandrogenism. Because virilization of affected females starts as soon as the sixth week of gestation[127], treatment has to be initiated as soon as pregnancy is documented[128-131]. Treatment initiated after nine weeks of gestation will be incompletely effective[132]; therefore, early diagnosis is required if prenatal treatment is desired. Chorionic villus sampling and rapid genotypic of fetal cells is performed at 11 weeks of gestation[133], and treatment is discontinued if genetic testing reveals a male or unaffected female fetus. Screening for the most common *CYP21A2* mutations identifies approximately 90% of the affected patients[46], but screening does not detect other forms of CAH. These procedures and treatments are costly and involve some risk to the mother. Earlier diagnosis appears to be possible by targeted massively parallel sequencing performed on cell-free fetal DNA circulating in maternal plasma at five weeks gestation[134,135], and this approach might facilitate the decision of whom to treat.

Dexamethasone prevents or reduces virilization in over 85% of prenatally treated girls[132]. On the other hand, data regarding maternal and fetal long-term safety are scarce[136]. In the absence of a diagnosis when treatment must commence, seven unaffected children receive treatment to prevent virilization in one affected female on average. Parents should receive counseling regarding potential side effects and give informed consent to treatment. If elected, treatment from an experienced team in research centers that monitor outcomes is recommended[29].

III. Summary and future directions

Adrenal biosynthesis of mineralocorticoids, glucocorticoids and androgen precursors follow specific enzymatic cascades in distinct, concentric adrenal zones, a design that optimizes steroid production efficiency. CAH results from autosomal recessive enzymatic defects in cortisol biosynthesis. The most common form is 21OHD, accounting for over 90% of CAH cases. The clinical spectrum ranges from severe or classic forms, of which 75% have both mineralocorticoid and glucocorticoid deficiency, to mild, nonclassic 21OHD, in which ACTH overstimulation compensates for the partial block in cortisol production. All forms are characterized by excessive adrenal androgen production, which parallels the severity of the enzymatic defect. Diagnosis of 21OHD is based on elevations of 17OHP and is included in standard newborn screening throughout the US and many other countries. Although this approach is excellent in distinguishing the classic forms and unaffected individuals, it suffers from false positive and negative results and poorer discrimination of intermediate severity cases from heterozygote carriers. Incorporation of other steroids upstream the enzymatic defect such as 21dF in the diagnostic panel, as well as wider use of second-tier mass spectrometry assays, might increase sensitivity and specificity in future.

Glucocorticoids and, when needed, mineralocorticoids, are the mainstay of treatment in 21OHD. These serve both in replacing the deficient steroids, as well as in suppressing the excessive adrenal androgen production. New treatments under study include sustained-release hydrocortisone and inhibitors of androgen biosynthesis. Balancing and accurately

monitoring treatment remains clinically challenging. 17OHP, AD and, in women, testosterone, have been utilized for treatment adjustment, but they do not always correlate well with clinical evidence of androgen excess. The identification and validation of adrenal-specific steroids and other molecules, which can be employed clinically as biomarkers of adrenal-derived androgen production, would be of major clinical utility to facilitate treatment monitoring.

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Key Points

1. Steroidogenesis in the adrenal gland reflects the zone-specific expression of enzymes, which comprise pathways to efficiently complete the biosynthesis of aldosterone, cortisol, and dehydroepiandrosterone sulfate.
2. The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency, in which a block in cortisol biosynthesis shifts precursors to pathways that make excess adrenal-derived androgens.
3. Non-classic 21-hydroxylase deficiency differs from the classic form in that cortisol deficiency and virilization of newborn girls are absent.
4. Treatment for classic 21-hydroxylase deficiency consists of glucocorticoid and mineralocorticoid replacement, and for both classic and non-classic disease, sufficient glucocorticoid is administered to correct the androgen excess.
5. Patients with 21-hydroxylase deficiency are prone to developing adrenal cortical adenomas and myelolipomas, as well as adrenal rest tumors in the testis or elsewhere.

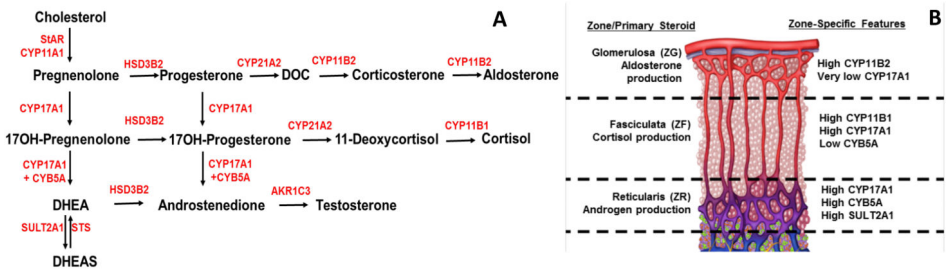

Figure 1.

A. Major adrenal steroid synthesis pathways. B. Adrenal zonation and enzyme expression pattern. StAR, steroidogenic acute regulatory protein; CYP11A1, side-chain cleavage enzyme; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; CYP21A2, 21-hydroxylase; CYP11B2, aldosterone synthase; CYP17A1, 17α-hydroxylase/17,20-lyase; CYP11B1, 11β-hydroxylase; CYB5A, cytochrome b_5; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; SULTA1/STS, steroid sulfotransferase type 2A1.

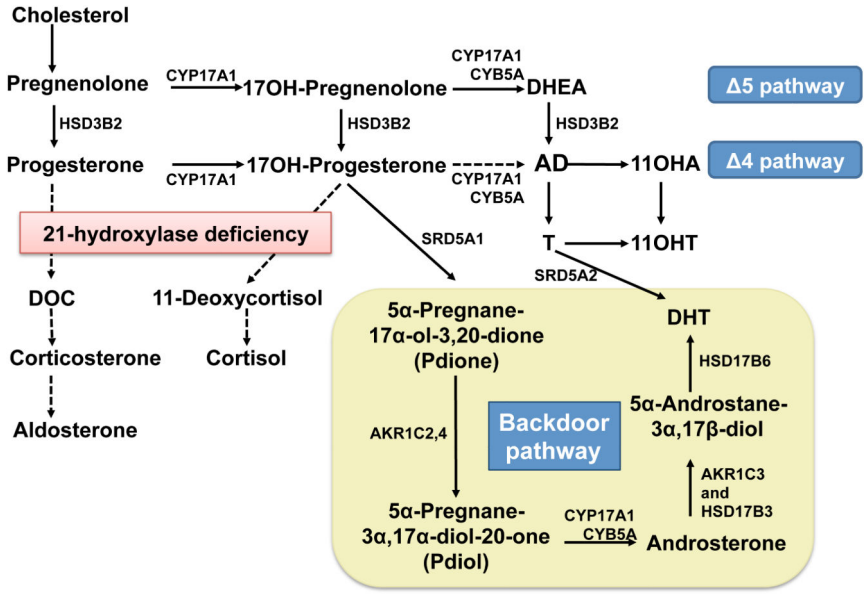

Figure 2.

Pathways of steroid hormone synthesis in 21-hydroxylase deficiency, including backdoor pathway and 11-oxygenated androgens. HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; CYP17A1, 17α-hydroxylase/17,20-lyase; CYB5A, cytochrome b_5; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; AKR1C2,4, aldo-keto reductase types 1C2 and 1C4; HSD17B6, 17β-hydroxysteroid dehydrogenase type 6 (an oxidative 3α-HSD); SRD5A1/2, 5α-reductase, types 1 and 2.

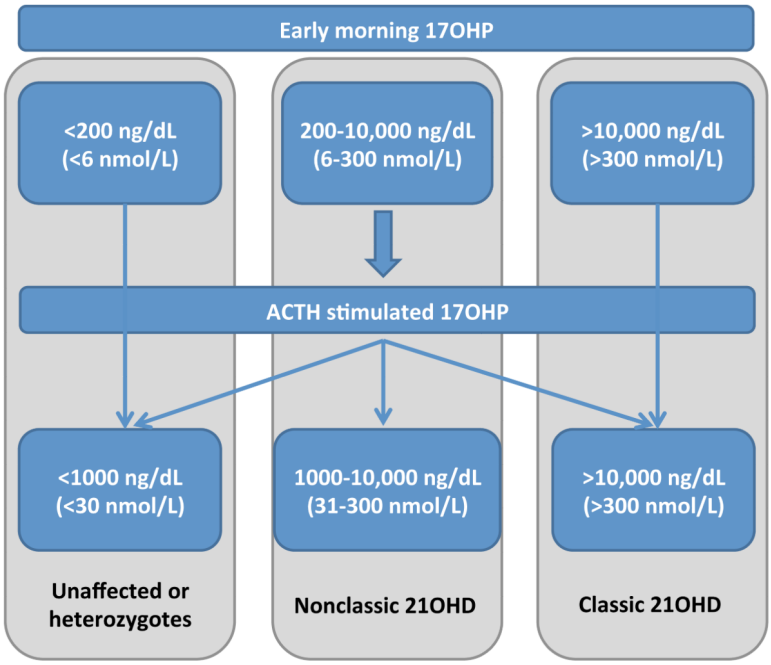

Figure 3.
Schematic evaluation of 21OHD based on baseline and stimulated 17OHP values.

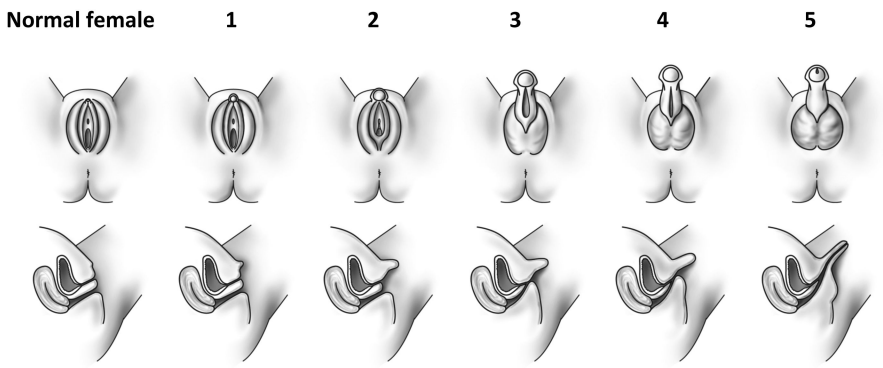

Figure 4.
Prader scale, female external genitalia viewed from above (top) and in cross-section (bottom).

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Table 1

Rare forms of congenital adrenal hyperplasia.

Defective enzyme	Gene/ Chromosome	Incidence & Populations	Clinical features	Laboratory findings
11β-hydroxylase (P450c11β)	*CYP11B1*/8q24.3	1:200,000 newborns High prevalence in Morrocan Jewish	Hypertension in most patients; hypokalemia; hyperandrogenemia; virilization	↑: 11DOC, 11-deoxycortisol, AD, T ↓: aldosterone, cortisol.
17-hydroxylase/ 17,20-lyase (P450c17)	*CYP17A1*/10q21-q22	1:50,000 newborns 2nd most common CAH form in Brazil	Hypertension, hypokalemia, and hypogonadism; 46,XX: primary amenorrhea; absence of secondary sexual characteristics 46,XY: undervirilization; abdominal testes	↑: progesterone, 11DOC, corticosterone; LH & FSH ↓: cortisol, DHEA, DHEAS, AD, T
3β-hydroxysteroid dehydrogenase type 2	*HSD3B2*/1p13.1	Rare	Volume depletion, hyponatremia, hyperkalemia 46,XX: mild clitoromegaly 46,XY: undervirilization from hypospadias to female-appearing	↑: Δ5 steroids-pregnenolone, 17OH-pregnenolone, DHEA, DHEAS ↓: cortisol, aldosterone
Lipoid CAH	*STAR*/8p11.2	Rare More frequent in Japanese, Palestinians, Koreans	Adrenal insufficinecy; enlarge lipid-laden adrenal glands; sexual infantilism	d All steroids decreased
Cholesterol side-chain cleavage enzyme (P450scc)	*CYP11A1/15q23-q24*	Isolated cases reports	Adrenal insufficiency; adrenal may appear absent	All steroids decreased
P450-oxidoreductase (POR)	*POR*/7q11.2	Rare More common in Japan and Korea	Volume depletion; skeletal malformations (Antley-Bixler); maternal virilization 46,XX: mild-to-moderate virilization 46,XY: undervirilization from hypospadias to female-appearing	Highly variable profiles, ; multiple partial defects ↑: progesterone; 11DOC, corticosterone, 17OHP variably high ↓: cortisol, aldosterone, androgens, and estrogens

Table 2

Available corticoid formulations and suggested doses for adults

Type of steroid	Total daily dose (mg)	Number of doses/day
Hydrocortisone	15-25	2-3
Prednisone	5-7.5	2
Prednisolone	4-6	2
Dexamethasone	0.25-0.5	1
Fludrocortisone	0.05-0.2	1