Congenital Adrenal Hyperplasia Due to 21 Hydroxylase Deficiency: From Birth to Adulthood

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Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from deficiency of one of the enzymes required for cortisol synthesis in the adrenal cortex. The most frequent of these is steroid 21-hydroxylase deficiency, accounting for more than 90% of cases. Affected patients cannot synthesize cortisol efficiently. Thus the adrenal cortex is stimulated by corticotropin (ACTH) and overproduces cortisol precursors. Some precursors are diverted to sex hormone biosynthesis, causing signs of androgen excess including ambiguous genitalia in newborn females and rapid postnatal growth in both sexes. In the most severe “salt wasting” form of CAH (~75% of severe or “classic” cases), concomitant aldosterone deficiency may lead to salt wasting with consequent failure to thrive, hypovolemia, and shock. Newborn screening minimizes delays in diagnosis, especially in males, and reduces morbidity and mortality from adrenal crises. CAH is a recessive disorder caused by mutations in the CYP21 (CYP21A2) gene, most of which arise from recombination between CYP21 and a nearby pseudogene, CYP21P (CYP21A1P). Phenotype is generally correlated with genotype. Classic CAH patients require chronic glucocorticoid treatment at the lowest dose that adequately suppresses adrenal androgens and maintains normal growth and weight gain, and most require mineralocorticoid (fludrocortisone). Transition of care of older patients to adult physicians should be planned in advance as a structured, ongoing process.

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Keywords

► CAH
► CYP21A2
► glucocorticoid
► mineralocorticoid
► ambiguous genitalia

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Biochemistry

Steroid 21-hydroxylase (CYP21, also termed CYP21A2, P450c21) is a cytochrome P450 enzyme located in the endoplasmic reticulum. It catalyzes conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycorticisol, a precursor for cortisol, and progesterone to deoxycorticosterone, a precursor for aldosterone.

Thus, patients with 21-hydroxylase deficiency cannot synthesize cortisol efficiently, and thus the adrenal cortex is stimulated by corticotropin (ACTH) and overproduces cortisol precursors. Some of these precursors are diverted to sex hormone biosynthesis, which may cause signs of androgen excess including ambiguous genitalia in newborn
females and rapid postnatal growth in both sexes. Concomitant aldosterone deficiency may lead to salt wasting with consequent failure to thrive, hypovolemia and shock.

**Clinical Manifestations in Children**

There is a range of phenotypes. A severely affected form with a concurrent defect in aldosterone biosynthesis (“salt wasting” type) and a form with apparently normal aldosterone biosynthesis (“simple virilizing” type), are together termed “classic” 21-hydroxylase deficiency. A mild “nonclassic” form may be asymptomatic or associated with signs of postnatal androgen excess.²

Classic 21-hydroxylase deficiency is detected in ~1/16,000 births in most populations (reviewed in⁴). The nonclassic form occurs in ~0.2% in the general Caucasian population but is more frequent (1–2%) in certain populations such as Jews of Eastern European origin.

**Salt Wasting**

Approximately 75% of classic 21-hydroxylase deficiency patients cannot adequately synthesize aldosterone. Elevated progesterone may act as a mineralocorticoid antagonist, exacerbating the effects of aldosterone deficiency.³ Since aldosterone regulates urinary sodium resorption, untreated individuals excrete excessive sodium and develop hypovolemia and hyperreninemia. They cannot excrete potassium efficiently and are prone to hyperkalemia, especially in infancy. Cortisol deficiency contributes to poor cardiac function, poor vascular response to catecholamines, decreased glomerular filtration, and increased secretion of antiuretic hormone (reviewed in⁶). Thus, cortisol and aldosterone deficiency together cause hyponatremic dehydration and shock in inadequately treated patients. Moreover, development of the adrenal medulla is partially dependent on glucocorticoids, so that patients with salt wasting 21-hydroxylase deficiency may also have catecholamine deficiency, further exacerbating shock.⁷

**Ambiguous Genitalia**

In patients with 21-hydroxylase deficiency, the adrenals produce excess 17-OHP, 17-hydroxyprogrenolone, and progesterone, which are further metabolized to dehydroepiandrosterone (DHEA) and androstenedione. Once secreted, these substances are further metabolized to active androgens (testosterone and dihydrotestosterone). Adrenal secretion of excess androgen precursors does not significantly affect male sexual differentiation. In affected female patients, the urogenital sinus is in the process of septation when the fetal adrenal begins to produce excess androgens at ~7 weeks of gestation (reviewed in⁹). Androgens inhibit the formation of separate vaginal and urethral canals. Adrenal-derived androgens interact with androgen receptors in genital skin and induce 5α-reductase (SRD5A2) expression, increasing synthesis of dihydrotestosterone, thus causing clitoral enlargement, fusion of the labial folds, and rostral migration of the urethral/vaginal perineal orifice. However, internal Wolffian structures such as the prostate gland and spermatic ducts are usually not virilized, presumably because development of the Wolffian ducts requires markedly higher local concentrations of testosterone than the external genitalia. Nevertheless, severely affected female patients occasionally have some development of typically male internal genital structures. Thus, the typical result in severely affected girls is ambiguous or male appearing external genitalia with perineal hypospadias and chordee, but without palpable testes.

It should be pointed out that the fetal adrenal normally secretes high levels of DHEA sulfate after 8 weeks of gestation, raising the question of why normal females are not virilized. This is a consequence of the simultaneous increase in expression of placental aromatase (CYP19) which converts adrenal-derived androgens to estrogens, but is not expressed sufficiently early to prevent virilization in females affected with CAH. This makes sense teleologically; earlier expression of placental aromatase might interfere with masculinization of the genitalia in normal males.⁸

An additional mechanism that may exacerbate virilization of affected females is secretion by the adrenal gland of 5α-reduced steroids such as 5α-androstane-3α,17β-diol, which is an immediate precursor of dihydrotestosterone in androgen-target tissues.⁹

**Postnatal Virilization**

In inadequately treated patients, chronic exposure to high levels of sex hormones promotes rapid somatic growth (predominantly an androgen effect) and advanced skeletal age leading to premature epiphyseal fusion (predominantly an effect of extragonadal aromatization of androgens to estrogens).¹⁰ Pubic and axillary hair may develop early. Clitoral growth may continue in girls. Young boys may have penile growth despite small testes, since the androgens are adrenal in origin. Chronic exposure to androgens may activate the hypothalamic-pituitary-gonadal axis causing centrally-mediated precocious puberty.²

**Growth**

Linear growth is affected even with close therapeutic monitoring. Based on meta-analysis of data from over 30 centers, adult heights in classic patients average 1.4 standard deviations below the population mean, or 1.0 standard deviations below expectations adjusted for parental height.¹¹ Both under-treatment and over-treatment put patients at risk for short stature, the former owing to premature epiphyseal closure induced by sex steroids, and the latter to glucocorticoid-induced inhibition of growth.¹²

**Presentation in Simple Virilizing Patients**

Simple virilizing patients do not synthesize cortisol efficiently but retain adequate aldosterone secretion, thus maintaining sodium balance. Whereas females are usually diagnosed shortly after birth due to genital ambiguity, the diagnosis may be delayed for several years in males in locales without newborn screening; affected boys are usually detected when they develop signs of androgen excess. Later diagnosis is associated with greater difficulty in achieving hormonal
control, abnormal tempo of puberty, and more severe compromise in adult height.

**Presentation in Nonclassic Patients**
Nonclassic patients produce normal amounts of cortisol and aldosterone at the expense of mild-to-moderate overproduction of sex hormone precursors. A few nonclassic cases are detected by newborn screening programs, but most are missed. It is not known what proportion of cases ascertained in this manner eventually become symptomatic. Based on family studies, many patients with nonclassic disease never develop overt androgen excess. Some children grow rapidly or have advanced bone age, and some prematurely develop pubic or axillary hair.

**Clinical Manifestations in Adults**

**Psychosexual Issues**
Females with classic forms of CAH are exposed to excess androgens during prenatal and postnatal life, which could affect the brain. Classic female patients show higher rates of gender-atypical behavior; they have decreased interest in maternal behavior, ranging from lack of doll play in early childhood to lack of interest in childrearing. As a group, they show variably masculinized behavior in regards to play, playmates, body movements and occupational preferences. There is also increased prevalence of homosexuality and bisexuality. These findings have a dose–response relationship with disease severity.

Impaired sexual function occurs frequently in women with classic CAH; inadequate vaginal reconstruction, reduced clitoral sensitivity, and concerns about the appearance of genitalia could all contribute to this and could negatively influence the achievement of steady relationships, marital status and fertility. However, there are discrepancies between patients’ perception of the impact of the condition on their sexual life and what health professionals would assume from clinical examination. Impaired sexual function is correlated with disease severity, patients carrying CYP21 mutations predicting total impairment of enzymatic activity scored lower on sexual function and satisfaction with their sexual life compared with those carrying mutations predicting moderate impairment.

The majority of women with classic CAH maintain a female gender identity. However, the proportion (up to 5%) who wish to change to the male gender is larger than the prevalence of female to male transsexualism in the general population. It is mainly related to inadequate suppression of adrenal androgens with glucocorticoid therapy and to delays in gender assignment, suggesting postnatal effects rather than prenatal androgen exposure.

**Fertility in Females**
The fertility rate is reduced in CAH females, and generally is lowest among salt-wasting patients and least impaired in nonclassic patients. Factors that contribute to decreased fertility include: unsatisfactory intercourse due to an inadequate vaginal introitus, anovulatory cycles due to adrenal androgen excess or gonadotrophin suppression by glucocorticoid overtreatment and increased progesterone levels during the follicular phase. However, most studies did not disclose the number of patients attempting to conceive. In a United Kingdom study, 23 of 106 women tried to conceive, of whom 91% were successful, with similar rates between patients with the salt-wasting and simple-virilizing forms.

The fertility rate is higher in patients with the nonclassic form. A retrospective multicentric study reported 203 pregnancies among 101 patients, 68% of which occurred before the introduction of glucocorticoid treatment; however, spontaneous miscarriages were more common in pregnancies conceived prior to glucocorticoid therapy.

**Fertility in Males**
Fertility in men with classic forms has not been routinely assessed, but appears to be reduced. Recent data from the United Kingdom showed that 37% of males with classic CAH had attempted to father children and 67% of these had been successful. In a Finnish study, the child rate of males with CAH was only 20% that of the general population. The main conditions that lead to infertility are hypogonadotropic hypogonadism due to glucocorticoid overtreatment and due to poor hormonal control with increased adrenal androgens and/or the presence of testicular adrenal rest tumors (TARTs).

TARTs are benign tumors arising from adrenal cells within testicular tissue and are usually identified in patients with inadequate hormonal control. TARTs compress seminiferous tubules, causing obstructive azoospermia and irreversible damage of the surrounding testicular tissue. Most tumors are only detectable with imaging techniques such as ultrasound or magnetic resonance imaging. Histopathological examination demonstrates expression of ACTH-dependent steroidogenic pathways, but also the angiotensin II receptor and steroidogenic enzymes involved in mineralocorticoid biosynthesis. These findings suggest that ACTH and renin overstimulation could both contribute to TART development.

The prevalence of TARTs varied from 0 to 94%, depending on the population and the methodology used for their screening. Recently, TARTs were identified in 21% of boys with classic CAH 2 to 10 years old, suggesting that boys should be screened early for these tumors.

**Metabolic Abnormalities**
There is some evidence of increased prevalence of overweight/obesity (23–52%) as compared with the normal population in classic patients, especially females. Increased body fat has also been detected in adults with classic forms of CAH using dual energy X-ray absorptiometry; this could contribute to insulin resistance and dyslipidemia. Long-acting glucocorticoids might promote the development of obesity; however, no study compares long- and short-acting glucocorticoids in the same series. Moreover, most reports do not evaluate cumulative glucocorticoid doses or the degree of 17-OHP suppression. Thus overtreatment, which could contribute to the development of obesity, cannot be ruled out.
Insulin insensitivity has also been described, along with a significantly higher rate of gestational diabetes, a predictive factor for the development of Type-2 diabetes. However, in this study, suppressed 17-OHP levels were found in at least one measurement in 58% (15/26) of patients. On the other hand, the metabolic profile of 30 untreated simple virilizing adult females showed higher BMI, insulin resistance index, serum triglycerides, and lower HDL-cholesterol than control subjects. These data suggest that in classic patients, impaired insulin sensitivity may be associated with overtreatment and also with undertreatment, the latter resulting in increased androgen levels.

There is little evidence of dyslipidemia in classic patients and most studies show normal lipid profiles. Although increased body fat is associated with dyslipidemia, overweight and obese classic adults have lipid profiles similar to those of patients with normal BMI. A higher HDL/LDL ratio was observed in a Swedish series among females older than 30 years of age in comparison with the normal population.

One study showed hypercholesterolemia in a significant percentage of adult classic patients (46%); however, in this series a considerable percentage of obesity (41%) and overweight (37%) were observed associated with suppressed 17OH-progesterone levels (<12 nmol/L), which could account for this finding.

Higher BMI is often associated with hypertension (as is mineralocorticoid overtreatment); but 24-hour blood pressure monitoring was normal in 20 classic patients and none presented with left ventricular hypertrophy.

## Bone Mineral Density

CAH patients receiving long-term glucocorticoid therapy are at risk for decreased bone mineral density. Impaired bone mineral density has been observed in some CAH patients; a T score lower than –2.5 SD was identified in up to 18% of patients and between –2.5 and –1.0 SD in 13 to 61% of patients, while others reported no significant differences between patients and the normal population.

The increased androgen secretion and higher BMI frequently observed in classic patients could have a protective effect. These discordant results may reflect the analysis of small sample sizes of heterogeneous cohorts, which include prepubertal and young adult patients following different glucocorticoid regimens. Data regarding older adults remain scarce.

Osteoporosis is a risk factor for fractures; one study found a higher frequency of fractures in a series of 61 classic women 18 to 63 years of age, compared with age-matched controls.

## Diagnosis

### Newborn Screening

Classic 21-hydroxylase deficiency is characterized by markedly elevated serum levels of 17-OHP, the main substrate for the enzyme. Basal 17-OHP values measured by radioimmunoassay usually exceed 10,000 ng/dl (300 nmol/L) in affected infants, whereas normal newborn levels are below 100 ng/dl (3 nmol/L). This makes it possible to screen newborns for this disorder using dried blood on filter paper; this is now mandated in all 50 American states. Screening minimizes delays in diagnosis, especially in males, and reduces morbidity and mortality from adrenal crises (reviewed in).

To ensure that no infant with classic 21-hydroxylase deficiency is missed, normal limits must be set so low that the positive predictive value of an abnormal 17-OHP screening test is only 2%. The high rate of false positive values not only increases the real cost of screening, but also causes psychological distress to the parents pending repeat testing. Delays in accurate diagnosis can lead either to unnecessary steroid therapy, or to failure to institute therapy in a timely manner.

Many sick or premature infants have elevated 17-OHP levels without having inborn errors in steroid biosynthesis, especially at gestational ages less than 31 weeks. To improve accuracy, some screening programs have set reference levels for serum 17-OHP in infants based on weight and gestational ages. Measurement of a ratio of the sum of 17-OHP and 21-deoxycortisol to cortisol by tandem mass spectrometry may improve both sensitivity and specificity of screening.

Other hormones that are usually elevated in 21-hydroxylase deficiency include progesterone, androstenedione, and to a lesser extent testosterone. An atypical steroid, 21-deoxycortisol, is also elevated and may be particularly useful for identifying heterozygous carriers; it may be assayed by liquid chromatography/tandem mass spectrometry, but this is not routinely available.

Mutation analysis (see next section) can confirm the diagnosis and is used in some newborn screening programs. It is available commercially in the United States but is expensive and often not completely covered by insurers.

### Specific Diagnosis

The gold standard for diagnosis of CAH is a cosyntropin stimulation test. Existing norms are for tests employing a pharmacologic dose of 0.125 to 0.25 mg cosyntropin (ACTH1-24), which maximally stimulates the adrenal cortex. This diagnostic test is distinguished from the low-dose cosyntropin stimulation test often used to evaluate the integrity of the hypothalamic-pituitary-adrenal axis.

The severity of hormonal abnormalities depends on the type of 21-hydroxylase deficiency. Patients with salt-wasting disease have the highest 17-OHP levels (up to 100,000 ng/dl, or 3,000 nmol/L, after ACTH stimulation), followed by simple virilizing patients, who usually have somewhat lower levels (10 to 30,000 ng/dl, or 300 to 1000 nmol/L). Patients with nonclassic disease have more modest elevations (1,500 to 10,000 ng/dl, or 50 to 300 nmol/L), especially in the newborn period. Random measurements of basal serum 17-OHP are often normal in nonclassic patients unless performed in the early morning.

Females with ambiguous genitalia are usually evaluated shortly after birth, before results of the newborn screen are available. Approaches to evaluating children with ambiguous...
Genitalia are reviewed elsewhere. In brief, it is important to quickly determine the genetic sex and internal anatomy of the infant, which is best accomplished by a thorough physical examination, a pelvic ultrasound evaluation (if a competent operator is available), and counting of sex chromosomes on interphase nuclei by fluorescent in situ hybridization or by microarray techniques. These evaluations can generally be completed within one working day. CAH due to 21-hydroxylase deficiency should be suspected in any 46,XX virilized female with normal internal Mullerian structures (i.e., a uterus detected on sonography).

When CAH is suspected based on ambiguous genitalia, hormonal testing should be deferred until after the first 24 hours of life. There is a high incidence of both false positive and false negative results when samples are obtained immediately after birth. Conversely, if the index of suspicion for CAH is high (ambiguous genitalia in females, markedly elevated 17-OHP on the newborn screen in either sex, and/or electrolyte abnormalities), treatment should be instituted immediately without waiting for the results of a cosyntropin stimulation test. Whether or not to conduct stimulation testing under these circumstances will depend on the local situation. Large pediatric referral hospitals with an on-call pediatric endocrinologist may be able to conduct such testing quickly. However, in many institutions the risks of delaying treatment to perform the test may outweigh the benefits, particularly in sick infants with abnormal electrolytes.

In performing stimulation testing, it should be kept in mind that 17-OHP may be elevated in other, more rare enzymatic defects, particularly 11β-hydroxysteroid dehydrogenase deficiency, 3β-hydroxysteroid dehydrogenase deficiency, and P450 oxidoreductase deficiency (Antley-Bixler syndrome). To fully differentiate the various enzymatic defects potentially causing CAH, ideally 17-OHP, cortisol, deoxycorticosterone, 11-deoxycorticisol, and 17-OH-pregnenolone should be measured at 0’ and 60’ with at least one measurement each of DHEA and androstenedione. If blood volume is an issue in small infants, a sample is collected only at 60’. Precursor: product ratios are particularly useful in distinguishing the different enzymatic defects. If second-tier screening with LC-MS/MS is employed, all relevant steroids can be measured.

As mentioned previously, patients with salt wasting have abnormal serum electrolytes, inappropriately low aldosterone, and elevated plasma renin. The latter tests are generally not useful for diagnosis in the neonatal period; aldosterone assay results often take several days to return, and renin levels (measured either as renin activity or directly) are normally higher in neonates than in older children. Many clinicians do find renin helpful for monitoring subsequent adequacy of fludrocortisones replacement (see below).

**Genetics**

**Mutations**

Steroid 21-hydroxylase deficiency is an autosomal recessive disorder caused by mutations in the CYP21 (CYP21A2) gene, which is located in the highly polymorphic HLA histocompatibility complex on chromosome 6p21.3 along with a pseudogene, CYP21P (CYP21A1P) (reviewed in). Although CYP21 and CYP21P are 98% identical in nucleotide sequence, the latter has accumulated several mutations that totally inactivate its gene product. These include an 8-base-pair deletion in exon 3, a frameshift in exon 7, and a nonsense mutation in exon 8. Additional mutations in CYP21P affect pre-mRNA splicing or amino acid sequence. Most mutations causing 21-hydroxylase deficiency arise from two types of recombination between CYP21 and CYP21P. Approximately 75% represent deleterious mutations found in the pseudogene that are transferred to CYP21 during mitosis by a process termed gene conversion. About 20% are meiotic recombinations that delete a 30-kilobase gene segment encompassing the 3’ end of the CYP21P pseudogene, all of the adjacent C4B complement gene, and the 5’ end of CYP21. This produces a non-functional chimeric pseudogene. Over 165 additional mutations comprise the remaining 5%.

In patients, 1 to 2% of affected alleles are de novo mutations not carried by either parent. Moreover, many patients carry more than one mutation on each allele because of the high rate of gene conversion. It is therefore important to ascertain parental genotypes for prenatal counseling and to set phase on detected mutations.

**Phenotype–Genotype Correlations**

Correlations between CYP21 genotype and phenotype have been studied in various ethnic and racial groups and reviewed in. CYP21 mutations can be grouped into three categories according to the level of enzymatic activity predicted from in vitro mutagenesis and expression. The first group consists of mutations such as deletions or nonsense mutations that totally ablate enzyme activity; these are most often associated with salt-wasting disease. The second group of mutations, consisting mainly of the missense mutation Ile172Asn (I172N), yields enzymes with 1 to 2% normal activity. These permit adequate aldosterone synthesis and are characteristic of patients with simple virilizing disease. A mutation in the second intron (nucleotide 656A to G, transferred from CYP21P by gene conversion) comprises 25% of all classic 21-hydroxylase deficiency alleles and usually results in abnormally spliced mRNA transcripts. However, a small amount of the mRNA is normally spliced, and thus this mutation is associated with both salt-wasting and simple virilizing disease.

The final group of mutations includes Val281Leu (V281L) and Pro30Leu (P30L), which produce enzymes retaining 20 to 60% of normal activity; these are associated with nonclassic disease.

When 21-hydroxylase deficiency phenotype is quantitated using 17-OHP levels or scores for signs of androgen excess or salt wasting, 80 to 90% of phenotypic variation is accounted for by CYP21 genotype (i.e., allelic variation). Compound heterozygotes for two different CYP21 mutations usually have a phenotype compatible with the milder of the gene defects.
Management

Glucocorticoid Replacement

Children

Patients with classic 21-hydroxylase deficiency require chronic glucocorticoid treatment to inhibit excessive secretion of CRH and ACTH by the hypothalamus and pituitary and reduce elevated adrenal sex steroids (reviewed in 3). In children, the preferred drug is hydrocortisone (i.e., cortisol itself) in maintenance doses of 10 to 20 mg/M²/day in three divided doses. Hydrocortisone's short half-life minimizes growth suppression and other adverse side effects of longer acting, more potent glucocorticoids such as prednisone and dexamethasone. Because of the short half-life, a single daily dose of hydrocortisone is ineffective in regulating adrenocortical secretion. There is divergence of opinion regarding whether to administer 3 equal doses over the day, or provide more hydrocortisone in the morning (the time of the normal diurnal ACTH and cortisol peaks) or the evening, to attempt to suppress the morning ACTH peak. There appears to be little difference between such regimens in practice.42

Stress doses of up to 100 mg/M²/day are given during adrenal crises and life-threatening situations. Even maintenance doses exceed physiologic cortisol secretion (7–9 mg/M²/day in neonates and 6–8 mg/M²/day in children and adolescents). Treatment efficacy is best monitored by measuring 17-OHP and androstenedione levels at a consistent time in relation to medication dosing. Children should also have an annual bone age X-ray and careful monitoring of linear growth.

The goal is to use the lowest glucocorticoid dose that adequately suppresses adrenal androgens and maintains normal growth and weight gain; generally <17 mg/M²/24h of hydrocortisone.12 One should not strive to normalize 17-OHP since this requires supraphysiologic glucocorticoid doses. Rather, 17-OHP levels should be partially suppressed to the range of 100 to 1000 ng/dl (3 to 30 nmol/L). Androstenedione and testosterone levels (the latter useful only in women and pre-pubertal children) should be maintained at a level appropriate for age and sex.

Treatment is not indicated in asymptomatic children with nonclassic 21-hydroxylase deficiency since potential adverse effects of glucocorticoids probably outweigh any benefits. Glucocorticoid treatment should be reserved for children with early onset and rapid progression of pubic and body hair, growth, and/or skeletal age.

Adults

Short-acting, intermediate-acting, or long-acting glucocorticoid formulations have been used in CAH adults. Among European endocrinologists, 36% use hydrocortisone (mean dose 13.75 mg/M²/day), 14% prednisolone (4.75 mg/day), and 33% dexamethasone (0.5 mg/day).20 The Endocrine Society recently endorsed the use of long-acting glucocorticoids in adulthood, such as a single daily dexamethasone dose (0.25–0.5 mg/day) or prednisone (5–7.5 mg/day divided into two doses).3 Particularly when aiming for normal ovulation to promote fertility, longer-acting glucocorticoids may be a more suitable option than short-acting hydrocortisone.

The mineralocorticoid actions of these glucocorticoids differ greatly; dexamethasone has no mineralocorticoid activity receptor whereas 40 mg of hydrocortisone is equivalent to 0.1 mg of fludrocortisone; consequently, dosage of mineralocorticoid should be reevaluated when changing the glucocorticoid.

Laboratory goals include normalization of androstenedione levels for men and of androstenedione and testosterone levels for females during the follicular phase of the menstrual cycle. Chronic normalization of 17-OHP levels should be avoided; values up to ~100 nmol/L (3,000 ng/dL) are acceptable when androgen levels are under control and the health of the patient is clinically satisfactory.43 In men, goals also include achieving normal gonadal function in the absence of TART. In patients with such tumors, the first therapeutic option is to temporarily intensify glucocorticoid replacement with dexamethasone (0.75–2 mg/day) to reduce tumor size by suppressing ACTH.43,44 Surgical resection of TARTs effectively controls testicular size and Leydig cell function but may not restore fertility.

Most nonclassic patients have normal cortisol responses to stress and treatment is indicated only for those who are symptomatic. Treatment with oral contraceptives alone may be sufficient in patients with menstrual abnormalities, acne or mild hirsutism, but, glucocorticoid treatment may decrease the risk of persistent anovulation even in those women not seeking fertility.45

Mineralocorticoid Replacement

Children

Infants with the salt-wasting form of 21-hydroxylase deficiency require mineralocorticoid (fludrocortisone acetate, usually 0.1 to 0.2 mg daily but up to 0.4 mg daily in sick neonates) and sodium chloride supplements (1–2 g sodium chloride, or 17–34 mmol sodium daily) in addition to glucocorticoid treatment. The sodium content of either breast milk or infant Eq. (8 mmol/L) is insufficient to compensate for sodium losses in these infants. Older infants and children usually do not require sodium chloride supplements, and they often have reduced fludrocortisone requirements.

Patients with the simple virilizing form of the disease by definition secrete adequate amounts of aldosterone, but nevertheless many are treated with fludrocortisone. This can aid in adrenocortical suppression, reducing the dose of glucocorticoid required to maintain acceptable 17-OHP levels. Blood pressure and plasma renin activity or direct rennin assays may be used to monitor mineralocorticoid and sodium replacement. Hypertension, edema, tachycardia and suppressed plasma renin signify overtreatment with mineralocorticoids. Excessive fludrocortisone may also retard growth.

Adults

Mineralocorticoid replacement is usually continued in adult life; however, adults require lower doses than infants, which may be explained by increases in mineralocorticoid
sensitivity, dietary sodium intake and activity of extradrenal enzymes that can 21-hydroxylate progesterone. There are no specific studies evaluating optimal doses and most adult patients receive 0.05 to 0.1 mg/day of fluocortisone. To titrate mineralocorticoid replacement, plasma renin activity and blood pressure in the sitting and standing positions are monitored.

Reproductive and Psychosexual Issues in Affected Females

Ambiguous Genitalia

Improvements in the surgical correction of genital anomalies over the past two decades have led to earlier use of single stage surgery between 2 and 6 months of life, a time when the tissues are maximally pliable and psychological trauma to the child is minimized. It is essential that such technically demanding surgery only be done by experienced surgeons. Patient advocacy groups have appealed to physicians to fully inform families of potential surgical pitfalls and to carefully consider if and when surgery should be done. Additionally, there is now heightened awareness of the need for psychological support for families with an affected child. Respect for patient’s privacy has led to fewer genital examinations during childhood and adolescence.

There are limited data regarding long-term follow-up of single-stage feminizing genitoplasty. Good morphological and functional results were achieved in ~68% of the cases in a cohort comprising 34 classic females after single-stage surgery. During transition of care, or when appropriate, the adequacy of the vaginal introitus should be evaluated. Although reoperation is sometimes required, the first option for treating vaginal stenosis is by dilation with acrylic molds.

Treatment during Pregnancy

Patients with classic CAH who become pregnant should continue their pre-pregnancy doses of glucocorticoids and mineralocorticoids; however, the glucocorticoids of choice are those inactivated by placental 11β-hydroxysteroid dehydrogenase Type 2 (e.g., hydrocortisone, prednisone, and prednisolone) to avoid fetal exposure. Symptoms of adrenal insufficiency rarely develop in pregnant patients, but glucocorticoid doses should be adjusted if clinically indicated. Blood pressure and glucose tolerance are monitored during pregnancy, labor, and delivery. Stress doses of glucocorticoids should be given during labor and delivery. Most patients with classic forms of CAH will require caesarean sections, because corrective surgery for ambiguous genitalia could prevent vaginal delivery.

Prenatal Diagnosis and Treatment

Preconception counseling should be offered to women with classic CAH desiring pregnancy, and prenatal genetic counseling should be offered to all families. Given that the carrier rate for classic alleles is 1.6% in the general population, a classic CAH patient has a 0.8% (1/120) chance of having a child with classic CAH. Moreover, two thirds of ascertained nonclassic patients carry one “classic” allele with one or more severe mutations. A nonclassic patient mating with a partner of unknown genetic status has a risk of giving birth to a child with classic CAH of ~0.66 × 0.016 × 0.25 = 0.0025 = 0.25% = 1/400.

Thus the partner of a CAH patient may wish to be genotyped prior to conception if the couple wishes to consider the somewhat controversial option of treating an at-risk pregnancy. Prenatal maternally administered dexamethasone crosses the placenta (dexamethasone is not inactivated by placental 11β-hydroxysteroid dehydrogenase), suppresses sex steroid secretion by the fetal adrenal, and thus ameliorates genital ambiguity in affected females compared with their older affected sisters (reviewed in).

However, affected females comprise only 1 of 8 fetuses when both parents are known carriers. To prevent genital virilization, prenatal therapy must be administered early in the first trimester. The need to treat eight at-risk pregnancies to benefit one affected female ethically requires a good risk-benefit ratio, but in fact the long-term safety of prenatal treatment remains uncertain. No congenital malformations have been attributable to such therapy, and the incidence of fetal deaths in treated pregnancies does not exceed that predicted for the general population. However, subtle effects of glucocorticoids might go unnoticed during early life, and indeed behavioral abnormalities in treated individuals have been observed by one center.

There is a variable incidence of maternal complications. Overt Cushing syndrome, excessive weight gain and hypertension have been reported in ~1% of treated pregnancies. Decreases in the dexamethasone dose in later pregnancy have not been systematically tested for efficacy.

Thus, families must be fully informed of the potential risks to mother and fetus and the potential lack of benefit to males and unaffected females. Treatment should be restricted to specialized centers with approved research protocols.

Novel Treatments

Additional Medical Management

Blockade of sex-steroid synthesis or action might permit glucocorticoid doses to be decreased. A four drug regimen consisting of low dose hydrocortisone, fludrocortisone, testosterone (an aromatase inhibitor to prevent estrogen-induced epiphyseal fusion), and flutamide (an androgen receptor blocker to prevent virilization) reduced the rate of bone age advancement and slowed weight and height velocity, compared with a standard regimen of higher dose hydrocortisone and fludrocortisone.

No serious adverse effects were observed although there was more central precocious puberty in the experimental group. A trial of growth hormone to promote growth, combined with a gonadotropin releasing hormone analog to delay central puberty, showed some potential for enhancing height outcome. None of these experimental therapies is currently recommended as standard of care.
Elective Adrenalectomy

Laparoscopic adrenalectomy with low-dose steroid replacement has also been proposed as an alternative to standard medical treatment. Proponents argue that Addison disease is easier to treat than CAH and does not interfere with growth and puberty. For females, elimination of adrenal androgen excess might reduce hirsutism and other stigmata. Opponents believe that adrenalectomy is too radical an approach for a medically treatable condition and leaves the patient more susceptible to sudden death. Adrenalectomy does not prevent development of gonadal adrenal rests caused by high levels of ACTH, is likely to increase skin pigmentation, and one pituitary adenoma has been reported. Moreover, loss of adrenal DHEA secretion may have adverse effects on mood and fatigue.

Transition of Care

Most pediatric centers transfer their patients with CAH to an internal medicine center when they are between 16 and 21 years old. This transition period is of paramount importance not only to ensure a good relationship between patient and new professional staff but also to reevaluate the goals of therapy for each patient, since the objectives are different from those in childhood. This transition should be planned in advance as a structured, ongoing process. Medical records should be provided, and should include information regarding clinical form, age at diagnosis, current and significant past treatment regimens, genital and other surgeries. Patients must transition to responsibility for their own care, including daily medication and stress dosing during illness. Thus it should be ascertained that adolescent and young adult patients have adequate knowledge about their disease, potential complications and the need for stress dosing.

Many patients prefer not to continue with multiple daily doses of hydrocortisone and in such cases, long-acting glucocorticoids may be offered; however, in both treatment modalities, patients should be screened for side effects of long-term glucocorticoid exposure. Therapy should be individualized based on clinical form, age, gender, prior history, other illness, and immediate goals.

Additional topics that must be discussed with affected females include sexuality, sexual function, and genital anatomy including the use of vaginal dilators and surgical procedures, when necessary. Other relevant topics in both sexes include mental health and genetic counseling.

Adult patients with classic forms require periodic evaluation of glucocorticoid and mineralocorticoid replacement, metabolic profile, bone health, and fertility. For females, the choice of treatment regimens also depends on their reproductive needs, sensitivity to androgens and progesterone. For males, screening for TARTs should be performed. Screening for adrenal tumors should also be considered in those patients with lack of adherence to treatment.

Treatment of nonclassic females is indicated only for those with symptoms, such as hirsutism, oligomenorrhea, acne, infertility, and adrenal nodules.

Conclusions

CAH is a relatively frequent and potentially fatal inherited disorder. Early recognition and treatment can prevent morbidity and mortality, and therefore newborns are screened for this disorder in many locales. Glucocorticoid and mineralocorticoid therapy make it possible for CAH patients to live a normal life span; glucocorticoid dosing must be carefully titrated to maximize adult height. Long term consequences of chronic glucocorticoid exposure may include obesity, insulin resistance, and decreased bone mineral density. Psychosexual and reproductive functioning in affected women may be affected, and efforts should be made to improve long term outcomes of genitoplasty. Advances in molecular biology increased the specificity of prenatal diagnoses, but prenatal treatment of affected females is not yet considered standard of care. CAH is a lifelong condition and particular attention should be given to transitioning patients to adult care providers, preferably a specialized multidisciplinary team.


