

# AMERICAN ACADEMY OF PEDIATRICS

Section on Endocrinology and Committee on Genetics

## Technical Report: Congenital Adrenal Hyperplasia

**ABSTRACT.** The Section on Endocrinology and the Committee on Genetics of the American Academy of Pediatrics, in collaboration with experts from the fields of pediatric endocrinology and genetics, developed this policy statement as a means of providing up-to-date information for the practicing pediatrician about current practice and controversial issues in congenital adrenal hyperplasia (CAH), including the current status of prenatal diagnosis and treatment, the benefits and problem areas of neonatal screening programs, and the management of children with nonclassic CAH. The reference list is designed to allow physicians who wish more information to research the topic more thoroughly.

**ABBREVIATIONS.** CAH, congenital adrenal hyperplasia; 21-OH, 21-hydroxylase; 17-OHP, 17 $\alpha$ -hydroxyprogesterone; AF, amniotic fluid; HLA, human leukocyte antigen; ACTH, adrenocorticotropic hormone.

Congenital adrenal hyperplasia (CAH) consists of a family of disorders caused by reduced activity of enzymes required for cortisol biosynthesis in the adrenal cortex. The most common defect is 21-hydroxylase (21-OH) deficiency, which accounts for >90% of all cases of CAH. Classic 21-hydroxylase deficiency is found in about 1:12 000 to 1:15 000 births; the frequency of nonclassic deficiency is unknown, although it may occur in up to 3% of individuals in certain groups. Clinical consequences of 21-OH deficiency arise primarily from overproduction and accumulation of precursors proximal to the blocked enzymatic step. These precursors are shunted into the androgen biosynthesis pathway, producing virilization in the female fetus or infant and rapid postnatal growth with accelerated skeletal maturation, precocious puberty, and short adult stature in both males and females. Approximately 75% of patients with classic 21-OH deficiency also have a defect in their ability to synthesize aldosterone. Such patients, especially undiagnosed male infants, may die during the newborn period of shock resulting from salt wasting.

Recent advances in molecular genetic analysis allow for prenatal diagnosis and treatment of at-risk fetuses. However, controversy remains regarding the efficacy and safety of prenatal intervention that attempts to minimize prenatal virilization in girls. Other controversial issues include the optimal regi-

men for postnatal treatments and the effects of long-term corticosteroid therapy on final height, sexual function, and fertility. Approximately 20 states include screening for CAH as a part of their newborn screening profiles. The cost-effectiveness of the programs in detecting patients who would not have been diagnosed before clinical manifestation of CAH continues to improve as new standards for levels of 17 $\alpha$ -hydroxyprogesterone (17-OHP) in premature infants, very sick infants, and infants younger than 24 hours decrease the rate of false-positive results.

This review is designed to provide current information on prenatal diagnosis and treatment, the status of newborn screening, methods of diagnosis of affected patients and heterozygote carriers, and newer treatment approaches for CAH.

### PRENATAL DIAGNOSIS AND TREATMENT

The objective of prenatal diagnosis and treatment of 21-OH deficiency is the prevention of prenatal virilization in affected female infants and the early recognition of the potential for salt wasting in the newborn infant.

#### Prenatal Diagnosis of 21-OH Deficiency

Prenatal prediction of CAH attributable to classic 21-OH deficiency is possible by using a number of modalities: determination of amniotic fluid (AF) hormone levels, human leukocyte antigen (HLA) typing of chorionic villus cells and/or AF cells, and molecular genetic studies of chorionic villus cells and AF cells. Advances in molecular genetic techniques have made molecular genetic studies the test of choice.

Prenatal diagnosis of CAH was first reported in 1965, based on elevated levels of AF 17-ketosteroids and pregnanetriol.<sup>1</sup> In 1975, the association between an elevated 17-OHP concentration in AF and the birth of an infant with salt-wasting CAH was reported.<sup>2</sup> Subsequent reports have confirmed the usefulness of AF 17-OHP concentrations for the prenatal diagnosis of classic CAH attributable to 21-OH deficiency.<sup>3-13</sup> Although amniocentesis has been performed routinely during the second trimester in women at risk of having an infant with CAH, elevated 17-OHP levels in AF obtained as early as 9 to 13 weeks in pregnancies with an affected fetus have been reported. Androstenedione levels ( $\Delta 4$ ), which also are elevated in pregnancies in which the fetus is affected with CAH, provide another diagnostic measurement.

Because the gene for 21-OH has been linked to the HLA system on chromosome 6, prenatal prediction of CAH may be made by HLA typing of cultured AF

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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cells and cultured chorionic villus cells.<sup>5,7,10,13-18</sup> Use of chorionic villus cells permits earlier identification of the affected fetus than is possible with amniocentesis. In a pregnancy in which the fetus has an HLA type identical to that of the index case with 21-OH deficiency, the fetus is predicted to be affected. The fetus that shares 1 parental haplotype with the index case is predicted to be a heterozygous carrier, and the fetus with both haplotypes different from the index case is predicted to be homozygous normal.

The preferred technique for prenatal diagnosis is molecular genetic analysis using DNA extracted from chorionic villus cells or amniocytes for analysis of *CYP21B*, *C4* and HLA class I and II genes.<sup>18-23</sup> Advances in these molecular techniques have made genetic characterization more reliable and rapid,<sup>24</sup> such that in most centers the analysis of fetal *P450c21B* genes from chorionic villus cells or amniocytes has largely replaced hormonal and HLA analysis in the prenatal diagnosis of CAH attributable to 21-OH deficiency.<sup>25</sup> Causative mutations can now be identified on 95% of chromosomes using Southern blot analysis and selective amplification of the *CYP21B* gene by polymerase chain reaction, followed by allele-specific hybridization with oligonucleotide probes for a panel of 9 known *CYP21B* mutations.<sup>26</sup> A newly developed, rapid, allele-specific polymerase chain reaction has been used for prenatal diagnosis.<sup>27</sup> Mutations not detected by this approach can be characterized by direct sequencing of *CYP21B* genes.<sup>28,29</sup> Determination of satellite markers also may be informative. De novo mutations, found in patients with CAH but not in parents, are found in 1% of disease-causing *CYP21B* mutations.<sup>28</sup> Accurate prenatal prediction requires the correct molecular genetic analysis of the index case and molecular genetic analysis and complete hormonal profiling of the parents.

#### **Prenatal Treatment of CAH Attributable to 21-OH Deficiency**

Prenatal treatment of CAH to prevent the virilization of an affected female fetus has been considered desirable by a number of investigators.<sup>2,30-33</sup> Because masculinization of the external genitalia begins at about 6 to 7 weeks of gestation (8 to 9 weeks after the last menstrual period),<sup>34,35</sup> suppression of the fetal pituitary-adrenal axis at no later than 6 weeks of gestation theoretically could prevent ambiguity of the external genitalia in the female fetus with classic CAH, whereas therapy after that time would prevent progression of virilization.

Successful prenatal treatment to ameliorate or prevent virilization of a female fetus with classic CAH attributable to 21-OH deficiency was first reported in 1984.<sup>36</sup> In 2 pregnancies at risk for classic salt-wasting CAH, the mothers were treated with hydrocortisone and dexamethasone, respectively. Subsequent amniocentesis demonstrated that both infants were girls and had HLA types identical to those of their affected siblings, and treatment was continued to term. At birth, the external genitalia were normal in the infant whose mother was given dexamethasone and minimally virilized in the infant whose mother received hydrocortisone. Postnatally, the diagnosis

of 21-OH deficiency was confirmed in both infants.<sup>36</sup> There are reports of >50 affected female infants in whom prenatal treatment with dexamethasone has been attempted. The dose of dexamethasone has ranged between 0.5 and 2 mg/d in 1 to 4 divided doses. Treatment was begun as early as the 4th week of pregnancy to as late as the 16th week. In some cases, treatment was interrupted for 5 to 7 days before amniocentesis, and, in a few cases, treatment was discontinued at 21 to 26 weeks.<sup>18,21-23,37-53</sup>

#### **Fetal Outcome**

Of the total number of cases for which data are available, treatment was considered successful for almost three fourths of the female infants; approximately one third had normal genitalia, and two thirds were described as being mildly virilized with clitoromegaly, partial labial fusion, or both. In slightly more than one fourth of all female infants treated, therapy was unsuccessful, and the infants had marked genital virilization.

The variability of the results has been attributed to a number of factors: inadequate dosage, interruption of treatment, delay in initiating treatment, variability in maternal metabolic clearance, and variability of placental metabolism of the administered glucocorticoid.<sup>23,50</sup> Variability in onset of fetal sexual differentiation and maternal noncompliance to therapy also must be considered.<sup>23,50</sup>

Spontaneous abortion, fetal demise during late pregnancy, intrauterine growth retardation, liver steatosis, hydrocephalus, agenesis of the corpus callosum, and hypospadias with unilateral cryptorchidism<sup>51</sup> have been reported occasionally when mothers received short-term treatment in unaffected pregnancies, as well as in affected pregnancies in which the mother received prolonged corticosteroid treatment. These events generally have not been considered related to the treatment or to the disease itself.<sup>17,45,49,50</sup> In a report of intrauterine growth retardation in an infant treated successfully for CAH, however, it was concluded that intrauterine growth retardation still should be considered "a possible fetal complication of treatment."<sup>46</sup> In long-term follow-up of most infants treated throughout the pregnancy or treated prenatally until midgestation,<sup>17,44-50</sup> development seems to be normal, and growth has been consistent with the family pattern and that of the other affected siblings.<sup>17,41,42,44,45</sup> Rare adverse events, including failure to thrive and psychomotor and psychosocial delay in development, have been observed.<sup>51</sup> Long-term follow-up is limited, however, and detailed neuropsychological evaluations have not been reported.

In a preliminary report, cognitive and behavioral development of young children aged 6 months to 5.5 years treated prenatally with dexamethasone because of risk for CAH was assessed by standard questionnaires completed by the mothers. The development of those children was compared with the development of children from untreated pregnancies at risk for CAH.<sup>52</sup> No significant differences in cognitive abilities or behavior problems were identified.<sup>50</sup> However, the demonstration of an increased

frequency of neurologically silent white matter abnormalities and temporal lobe atrophy in children and adults with CAH indicates that the long-term effects of glucocorticoids on the central nervous system are not fully known and must be evaluated carefully.<sup>54</sup> Although experimental treatment given to animals cannot be directly extrapolated to humans, high doses of dexamethasone administered to rhesus monkeys toward the end of gestation were associated with abnormalities of the fetal brain consisting of neuronal degeneration of hippocampal, pyramidal, and dentate regions.<sup>55</sup> Other animal studies have focused on long-term cardiovascular risks of prenatal dexamethasone treatment. Intrauterine growth retardation, lower kidney weight, oligonephronia, and the development of hypertension in adulthood have been demonstrated in rat pups whose mothers received dexamethasone prenatally.<sup>56–58</sup> These studies underscore the need for careful long-term outcome studies of prenatal dexamethasone treatment, in which treated mothers and infants are followed up to determine possible ill effects in later adult life.

### Maternal Complications of Prenatal Treatment

Maternal adverse effects of dexamethasone may be serious and long-lasting.<sup>23,44</sup> Reported adverse effects include edema, excessive weight gain, irritability, nervousness, mood swings, hypertension, glucose intolerance, chronic epigastric pain, gastroenteritis, cushingoid facial features, increased facial hair growth, and severe striae with permanent scarring.<sup>17,18,23,40,44–47,49,50</sup>

In a European survey, adverse effects occurred in approximately one third of women who were treated until delivery and for whom data were available.<sup>48</sup> Marked weight gain, reported in approximately 25%, was the most common problem.<sup>48</sup> The maternal adverse effects prompted decreasing the dosage or discontinuing treatment and may have resulted in non-adherence with therapy and unsatisfactory genital outcome for the infant.<sup>40,49</sup> Transient symptoms of glucocorticoid deficiency on tapering or discontinuing treatment have been reported rarely.<sup>17,41</sup> A recent report indicated that one third of the mothers who received dexamethasone treatment during pregnancy would not elect treatment in a future pregnancy.<sup>51</sup>

### Current Recommendations for Prenatal Diagnosis and Treatment

Prenatal diagnosis and treatment is performed most commonly in families with a previously affected child with CAH with a defined genetic defect.

Informed consent, in which the risks of possible maternal adverse effects, variable genital outcome, and possible but presently unknown long-term effects of dexamethasone treatment on the treated children are discussed, should be obtained from all parents seeking genetic counseling before prenatal diagnosis and treatment. Mothers with previous medical or mental conditions that may be aggravated by dexamethasone, such as psychosis, hypertension, overt diabetes, gestational diabetes, or toxemia,

should not be treated or should be treated only with extreme caution. Patients should be referred to centers with expertise in the prenatal management of pregnancies at risk for CAH. Treatment should be initiated by the fifth week of gestation with dexamethasone, at a dose of approximately 20 to 25  $\mu\text{g}/\text{kg}$  per day, given in 2 or 3 divided doses. Chorionic villus sampling during the 9th to 10th week of gestation for prenatal diagnosis should be performed with karyotyping, and, optimally, *HLA*, *CYP21B*, and *C4* gene analysis of chorionic villus cells. If chorionic villus sampling is performed during the 10th to 11th week, a small amount of AF can be obtained for hormonal analysis as well, to gain some measure of fetal adrenal suppression. If the fetus is a boy or an unaffected girl, treatment is discontinued. If the fetus is an affected girl, or if prenatal diagnosis by chorionic villus sampling is unsuccessful or not performed, treatment is continued. If necessary, for further clarification, amniocentesis can be performed at 15 weeks with genetic analysis of amniocytes and hormonal determination in the AF. If the fetus is an affected girl, treatment is continued to term. It is important to note that if the mother is receiving treatment with dexamethasone, hormonal analysis of AF is unreliable for prenatal diagnosis. Furthermore, because only 1 of 8 infants will be an affected girl, 7 of 8 infants will be treated unnecessarily for at least 12 weeks.

Maternal monitoring for physical, hormonal, and metabolic changes should begin at the initiation of treatment and should be continued throughout the pregnancy. The serum estriol level to evaluate adequacy of fetal adrenal suppression and the fasting blood glucose level should be determined monthly, and an oral glucose tolerance test should be performed during the second and third trimesters. In the presence of excessive weight gain, increased blood pressure, and glucose intolerance or other adverse effects, prompt intervention should be instituted. Consideration should be given to reducing the dosage of dexamethasone during the second and third trimesters.

Maternal treatment seems to prevent or reduce virilization in approximately 75% of affected female fetuses but has not been uniformly successful in all pregnancies. Its efficacy and safety remain to be fully defined. It should be offered only to patients who have a clear understanding of the possible risks and benefits and who are able to comply with the need for close monitoring throughout pregnancy and the need for long-term follow-up of the infants, children, and adults treated prenatally.

### NEONATAL SCREENING

The major objectives of newborn screening for CAH attributable to 21-OH deficiency are to identify infants at risk for the development of life-threatening adrenal crisis and to prevent the incorrect male sex assignment of affected female infants with ambiguous genitalia. The former is particularly important for affected boys whose initial manifestation may be adrenal crisis. In addition, early identification will permit the monitoring and treatment of affected in-



infants and children to prevent postnatal exposure to excessive androgens and the accompanying clinical manifestations. In 1977, newborn screening for 21-OH deficiency became possible after development of the method to measure 17-OHP in a heel-stick capillary blood specimen on filter paper. A pilot newborn screening program was developed in Alaska shortly thereafter. National and regional screening programs now have been developed worldwide, and in almost 20 states.<sup>59–61</sup> Data on >8 million neonates screened are available. The disorder occurs in 1 of 21 000 newborns in Japan, 1 of 10 000 to 16 000 in Europe and North America, and 1 of 300 in Yupik Eskimos of Alaska. About 75% of affected infants have the salt-losing, virilizing form, and 25% have the simple virilizing form of the disorder. The nonclassic form is not detected reliably by newborn screening.

### Newborn Screening Procedures and Cost Analysis

Neonatal screening for CAH requires the following procedures for optimal efficiency and effective screening results: 1) early sample collection, ideally between 2 and 3 days of life; 2) immediate and reliable analysis of 17-OHP levels after sample collection; 3) optimally chosen 17-OHP cutoff levels that distinguish affected from unaffected newborns; 4) immediate and clear communication of presumptive positive results to the appropriate health care professional and to family members; and 5) diagnostic confirmation of newborns with positive screening results.

All CAH newborn screening programs use the measurement of 17-OHP in a filter paper blood spot sample obtained by the heel-stick technique as used for newborn screening of other disorders. The concurrent screening test procedures for disorders such as phenylketonuria and congenital hypothyroidism, which were established before the initiation of CAH screening, seem to have influenced the age at which CAH screening samples were collected in many programs. Although most screening samples for CAH had been collected between 3 and 5 days after birth,<sup>59,62</sup> recent practices of early discharge from the nursery and increased numbers of deliveries at birthing centers have resulted in many screening samples being collected at 1 to 2 days after birth. This may result in an increased number of false-positive tests.

The majority of screening programs worldwide use a single screening test without retesting of questionable 17-OHP levels.<sup>62</sup> This single-screen method offers the advantage of expedited results but may cause inaccurate classification in borderline cases. A small number of programs perform a second screening test of the initial sample to confirm borderline cases identified in the first screening.<sup>62</sup> Although relatively time-intensive, this approach provides greater accuracy than the single-screen method. One program (Manitoba, Canada) collects and tests a second sample on request when 17-OHP levels are elevated above the cutoff level in the initial test.<sup>62</sup> A number of programs mandate 2 screenings and routinely obtain and test a second sample.<sup>62–64</sup> In addition to detecting infants with the salt-wasting form of

CAH and preventing life-threatening adrenal crisis by using results of the first screening, this approach is optimal for minimizing false-negative results by detecting newborns with the simple virilizing and mild forms of the disorder on the second screening who may not have been identified initially.<sup>59</sup>

### Laboratory Screening Assay Methods and Cutoff Levels

Three principal assay techniques are used for the initial screening of CAH in neonates: radioimmunoassay, enzyme-linked immunosorbent assay, and time-resolved fluoroimmunoassay. These assays measure the 17-OHP concentration in a filter paper blood spot sample obtained by the heel-stick technique without prior extraction or purification. The 17-OHP levels measured by direct fluoroimmunoassay are significantly higher than levels measured by radioimmunoassay after extraction. Screening fluoroimmunoassay may overestimate 17-OHP levels in low birth weight infants weighing <1500 g.<sup>65</sup> Although theoretically 17-OHP concentrations in newborns should be comparable regardless of the assay method, there is considerable variation in cutoff levels from one program to another. The 17-OHP cutoff levels that divide positive from negative screening test results have been established at greater than the 99th percentile of the mean level in healthy newborns or on the basis of a normal range established in that program or on the experience of other programs.<sup>62</sup> Other sources of variation include the different antibodies and reagents used in the assay systems, varying thickness and density of the filter paper used for sample collection, and, most significantly, the ethnic background of the reference newborns.

### Reliability of Screening Tests

The reliability of each screening program is based on evaluation of both the false-negative and false-positive rates. There have been extraordinarily few false-negative results in newborn screening worldwide.<sup>62</sup> The majority of reported false-positive results have been caused by low birth weight and premature birth, in which the 17-OHP levels are invariably higher. Therefore, separate normative reference levels should be established based on birth weight or gestational age to minimize an otherwise unacceptably high false-positive rate. In 1 study, application of multitiered weight-adjusted 17-OHP cutoff levels compared with a 2-tiered criterion reduced the number of false-positive results requiring immediate follow-up testing by >50%, and the rate was reduced by >90% among low birth weight infants.<sup>65</sup> Two-tier weight-adjusted cutoff levels are being used by many programs with acceptable false-positive rates,<sup>62</sup> but further modification of the test cutoff levels and recall procedures is necessary in programs with persistently high false-positive rates.

As more adequate reference data have been developed, 17-OHP cutoff levels in low birth weight infants have been adjusted, and the false-positive rates in preterm screening populations have improved.<sup>62,65,66</sup> Issues relating to false-positive results, however, including the cost of evaluating false-pos-

itive cases and the undesirable psychological effect on patients' families, continue to be problematic. Therefore, periodic review of 17-OHP cutoff levels is essential to minimize false-positive and false-negative rates and ensure high sensitivity and specificity of neonatal screening tests for CAH. Genotyping for mutations in *CYP21B* causing CAH has been suggested as an adjunct to newborn screening.<sup>67</sup>

### DIAGNOSIS

In classic 21-OH deficiency, serum levels of 17-OHP are markedly elevated. However, 17-OHP levels are normally high during the first 2 to 3 days after birth and may range as high as levels found in affected patients. By the third day, however, levels in healthy infants fall, and those in affected infants rise to clearly diagnostic levels. Ill, unaffected infants and premature infants may have elevated levels of 17-OHP. Serum concentrations of testosterone in girls and androstenedione in boys and girls also are elevated in affected infants. Salt losers may have low serum sodium and chloride levels, inappropriately increased urine sodium levels, and elevated levels of serum potassium and serum urea nitrogen. However, hyponatremia and hyperkalemia are usually not present before 7 days of age. Plasma levels of renin are elevated, and the serum aldosterone level is inappropriately low for the renin level.

In the late-onset variant of CAH, basal circulating levels of 17-OHP are not as high as in the classic form and may even be normal, especially if the specimen is not obtained in the morning. Therefore, for initial screening, blood specimens should be obtained between 7:30 and 8:30 AM. Elevated basal 17-OHP levels may suggest the diagnosis, but an adrenocorticotropic hormone (ACTH) test with measurement of serum cortisol and 17-OHP levels is necessary to confirm the diagnosis. A significant rise in the 17-OHP level 60 minutes after an intravenous bolus of 0.25 mg of ACTH (1–24) is diagnostic. The 17-OHP–cortisol ratio is markedly elevated, and there may be a blunted or absent response in cortisol.

### TREATMENT

Administration of glucocorticoids inhibits excessive production of androgens and prevents progressive virilization. A variety of glucocorticoids (hydrocortisone, prednisone, dexamethasone) and dosage schedules have been used for this purpose. Most often, hydrocortisone (10–20 mg/m<sup>2</sup> per 24 hours) is administered orally in 3 divided doses. There have been recent problems with consistent dosing with the liquid formulation of hydrocortisone. Tablets may give more reliable levels. Infants usually require 2.5 to 5 mg 3 times daily and children, 5 to 10 mg 3 times daily. The morning dose should be given as early as possible to blunt the early morning corticotropin increase that begins during the predawn hours. Doses must be individualized by monitoring growth, bone age, and hormonal levels. Patients with disturbances of electrolyte regulation (salt losers) and elevated plasma renin activity require a mineralocorticoid and sodium supplementation in addition to the glucocorticoid. Maintenance therapy with fludro-

cortisone acetate (Florinef) (0.05–0.3 mg daily) and sodium chloride (1–3 g) is usually sufficient to normalize plasma renin activity. Increased doses of glucocorticoid are indicated during periods of stress, such as infection or surgery, for salt-losing and non-salt-losing patients.

Non-salt-losing children, particularly boys, frequently are not diagnosed until 3 to 7 years of age, at which time osseous maturation may be 5 years or more in advance of chronologic age. Institution of treatment slows growth and osseous maturation to more nearly normal rates in some children. In others, especially if the bone age is 12 years or more, spontaneous gonadotropin-dependent puberty may occur as therapy with hydrocortisone suppresses production of adrenal androgens and permits release of pituitary gonadotropins if the appropriate level of hypothalamic maturation is present. This form of superimposed true precocious puberty may be treated with a long-acting potent luteinizing hormone–releasing hormone analog.

Patients with nonclassic 21-OH deficiency do not always require treatment. Many are asymptomatic throughout their lives, or symptoms may develop during puberty, after puberty, or postpartum. Traditionally, therapy with lower amounts of glucocorticoid than those required for patients with classic 21-OH deficiency have been used. Indications for treatment include bone age advancement, severe acne, hirsutism, menstrual irregularity, and infertility.

The protocol for monitoring these patients varies with personal preference. Measurements of 24-hour urinary levels of 17-ketosteroids and pregnanetriol are unnecessary. Serum levels of 17-OHP, androstenedione, testosterone, and renin, measured preferably between 7:30 and 8:30 AM, either before or shortly after taking the morning medication, usually provide adequate indices of control. Recent reports indicate that 17-OHP may be measured reliably and accurately at home using filter paper techniques.<sup>68</sup> Careful monitoring for signs of cortisol and androgen excess, growth and weight gain, pubertal development, and osseous maturation is important.

The administration of glucocorticoid must be lifelong for all patients with classic forms of CAH. More potent glucocorticoids tend to suppress growth more than hydrocortisone. However, after growth is completed, prednisone, given once or twice daily, or dexamethasone, given as a single dose at bedtime, may result in adequate suppression of androgens.

Heterozygous carriers of 21-OH deficiency have been identified by measuring the ratio of 17-OHP to 11-deoxycortisol or cortisol 60 minutes after an intravenous bolus injection of 0.25 mg of ACTH (1–24) and, in families with an affected individual, by HLA genotyping. Molecular characterization, alone or in combination with hormonal measurements and HLA genotyping, should be used when available for genetic counseling.

A number of clinical trials have been designed to evaluate the efficacy of new treatment modalities. These modalities should be considered experimental at this time.

Because it is recognized that patients with Addison's disease are more easily and successfully treated than patients with CAH, adrenalectomy for patients with salt-wasting 21-OH deficiency has been suggested as a possible mode of therapy. This would eliminate the difficult problems of achieving adequate suppression of adrenal androgens without giving excessive glucocorticoid, and without the rapid advancement of bone age and early virilization that occur with inadequate adrenal androgen suppression. Adrenalectomy has been performed for treatment of 21-OH deficiency. Long-term follow-up of a large number of patients will be necessary to determine the safety and efficacy of this mode of therapy.<sup>69</sup>

Preliminary use of a combination of an antiandrogen (to block androgen effect) and an aromatase inhibitor (to block conversion of androgen to estrogen) with a reduced hydrocortisone dose also has been reported.<sup>70,71</sup> Again, long-term studies are required to determine if this regimen will further improve the final outcome. The use of synthetic blockers of the corticotropin-releasing hormone and corticotropin receptors theoretically could provide a pharmacologic adrenalectomy and may provide additional future treatment options.

CAH is a chronic disease requiring lifelong monitoring and treatment. The diagnosis and treatment are complex, requiring specific training and expertise to individualize therapy. Thus, a pediatric endocrinologist ideally should be involved in the management of all children and adolescents with CAH. A high index of suspicion should be present in any infant with ambiguous genitalia and nonpalpable testes, especially in the presence of increased pigmentation of nipples, genitalia, and/or skin creases. A family history of early neonatal deaths or previously affected family members adds to the risk of having CAH. Markedly elevated levels of 17-OHP should prompt immediate evaluation in any newborn infant. Pediatricians should call their state department of health to determine if newborn screening for CAH is available. New molecular techniques permit early prenatal diagnosis and have made possible intervention to prevent prenatal virilization in affected female infants. Early diagnosis through newborn screening may avert salt-losing crises, particularly in affected boys, by permitting early initiation of therapy. Although glucocorticoid therapy is the mainstay of treatment, the outcome has not been optimal and therapeutic regimens vary. New approaches to treatment, including adrenalectomy, combination antiandrogen and aromatase inhibitors, and synthetic blockers of corticotropin-releasing hormone and corticotropin receptors are under investigation. Support for families is available through a national CAH group, The Magic Foundation, 1327 North Harlem Avenue, Oak Park, IL, 60302 (<http://www.magicfoundation.org>).

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