Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline

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Objective: We developed clinical practice guidelines for congenital adrenal hyperplasia (CAH).

Participants: The Task Force included a chair, selected by The Endocrine Society Clinical Guidelines Subcommittee (CGS), ten additional clinicians experienced in treating CAH, a methodologist, and a medical writer. Additional experts were also consulted. The authors received no corporate funding or remuneration.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions. The guidelines were reviewed and approved sequentially by The Endocrine Society's CGS and Clinical Affairs Core Committee, members responding to a web posting, and The Endocrine Society Council. At each stage, the Task Force incorporated changes in response to written comments.

Conclusions: We recommend universal newborn screening for severe steroid 21-hydroxylase deficiency followed by confirmatory tests. We recommend that prenatal treatment of CAH continue to be regarded as experimental. The diagnosis rests on clinical and hormonal data; genotyping is reserved for equivocal cases and genetic counseling. Glucocorticoid dosage should be minimized to avoid iatrogenic Cushing's syndrome. Mineralocorticoids and, in infants, supplemental sodium are recommended in classic CAH patients. We recommend against the routine use of experimental therapies to promote growth and delay puberty; we suggest patients avoid adrenalectomy. Surgical guidelines emphasize early single-stage genital repair for severely virilized girls, performed by experienced surgeons. Clinicians should consider patients' quality of life, consulting mental health professionals as appropriate. At the transition to adulthood, we recommend monitoring for potential complications of CAH. Finally, we recommend judicious use of medication during pregnancy and in symptomatic patients with nonclassic CAH. (***J Clin Endocrinol Metab* 95: 4133–4160, 2010)**

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Abbreviations: BMD, Bone mineral density; CAH, congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DSD, disorders of sexual development; GC, glucocorticoid; GnRHa, GnRH agonist; HC, hydrocortisone; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; LC-MS/MS, liquid chromatography followed by tandem mass spectrometry; MC, mineralocorticoid; NCCAH, nonclassic CAH; 17-OHP, 17-hydroxyprogesterone; PRA, plasma renin activity; QoL, quality of life; SDS, SD score; US, ultrasound.

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Page 1 of 28

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Definition, Pathophysiology, and Morbidities of Congenital Adrenal Hyperplasia (CAH)

CAH is a group of autosomal recessive disorders characterized by impaired cortisol synthesis. The incidence ranges from 1:10,000 to 1:20,000 births (1–4) and is more prevalent in some ethnic groups, particularly in remote geographic regions (*e.g.* Alaskan Yupiks). The most common form of CAH is caused by mutations in *CYP21A2*, the gene encoding the adrenal steroid 21-hydroxylase enzyme (P450c21) (5, 6). This enzyme converts 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and progesterone to deoxycorticosterone, respective precursors for cortisol and aldosterone. Because this enzyme deficiency accounts for approximately 95% of CAH, we will discuss only 21-hydroxylase deficiency here. The cortisol synthetic block leads to corticotropin stimulation of the adrenal cortex, with accumulation of cortisol precursors that are diverted to sex hormone biosynthesis (Fig. 1). A cardinal feature of classic or severe virilizing CAH in newborn females is genital ambiguity. If the disorder is not recognized and treated, both girls and boys undergo rapid postnatal growth and sexual precocity or, in the case of severe enzyme deficiency, neonatal salt loss and death. About 75% of classic CAH cases suffer aldosterone deficiency with salt wasting, failure to thrive, and potentially fatal hypovolemia and shock (9).

In addition to the so-called classic salt-wasting and simple virilizing forms of CAH, there is also a mild nonclassic form, which may show variable degrees of postnatal androgen excess but is sometimes asymptomatic (10). The mild subclinical impairment of cortisol synthesis in nonclassic CAH (NCCAH) generally does not lead to Addisonian crises.

Nonclassic forms of CAH are more prevalent, occurring in approximately 0.1–0.2% in the general Caucasian population but in up to 1–2% among inbred populations, such as Eastern European (Ashkenazi) Jews (11).

Disease severity correlates with *CYP21A2* allelic variation. Genotyping individuals with CAH is fraught with error due to the complexity of gene duplications, deletions, and rearrangements within chromosome 6p21.3 (12). More than 100 *CYP21A2* mutations are known (13), but large deletions and a splicing mutation (intron 2, −13 from splice acceptor site, C-G substitution) that ablate enzyme activity comprise about 50% of classic CAH alleles (14, 15). A nonconservative amino substitution in exon 4 (Ile172Asn) that preserves approximately 1–2% of enzyme function is associated with simple virilizing classic CAH. A point mutation in exon 7 (Val281Leu) that preserves 20–50% of enzyme function (16) accounts for about 70% of NCCAH alleles (17, 18). Because many patients are compound heterozygotes for two or more different mutant *CYP21A2* alleles, a wide spectrum of phenotypes may be observed (15).

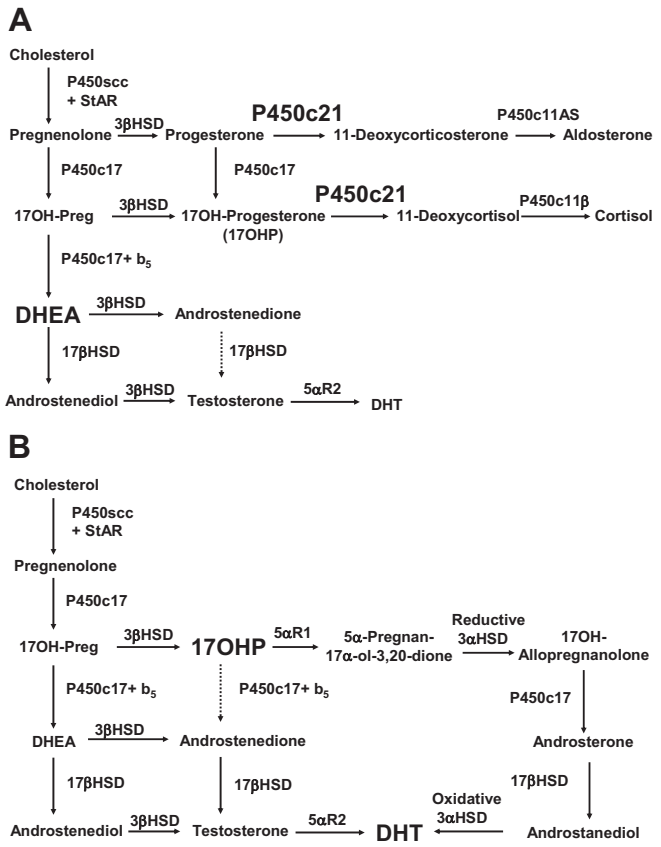

FIG. 1. A, Normal fetal adrenal steroidogenesis. Because the fetal adrenal has low levels of 3β-HSD, most steroidogenesis is directed toward DHEA (and thence to DHEA-sulfate), but small amounts of steroid enter the pathways toward aldosterone and cortisol. The adrenal 21-hydroxylase, P450c21, is essential in both pathways. The adrenal can make small amounts of testosterone via 17β-HSD. B, In the absence of the 21-hydroxylase activity of P450c21, three pathways lead to androgens. First, the pathway from cholesterol to DHEA remains intact. Although much DHEA is inactivated to DHEA-sulfate, the increased production of DHEA will lead to some DHEA being converted to testosterone and dihydrotestosterone (DHT). Second, although minimal amounts of 17-OHP are converted to androstenedione in the normal adrenal, the huge amounts of 17-OHP produced in CAH permit some 17-OHP to be converted to androstenedione and then to testosterone. Third, the proposed backdoor pathway depends on the 5α and 3α reduction of 17-OHP to 17OH-allopregnanolone. This steroid is readily converted to androstanediol, which can then be oxidized to DHT by the reversible 3α-HSD enzyme. Although first discovered in marsupials, mass spectrometric examinations of human urinary steroid metabolites indicate this pathway may also occur in the human adrenal (7, 8).

1.0 Newborn screening

See links to *Resources for Newborn Screening* in Supplemental Data, Appendix 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

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Recommendation

1.1 We recommend that screening for 21-hydroxylase deficiency be incorporated into all newborn screening programs (**1**|⊕⊕○○), using a two-tier protocol (initial immunoassay with further evaluation of positive tests by liquid chromatography/tandem mass spectrometry).

1.1 Evidence

CAH is a disease suited to newborn screening because it is common and potentially fatal. Early recognition and treatment can prevent morbidity and mortality. As of 2009, all 50 states in the United States and 12 other countries screen for CAH. Screening markedly reduces the time to diagnosis of infants with CAH (19–22). Morbidity and mortality are reduced due to early diagnosis and prevention of severe salt wasting. Because undiagnosed infants who die suddenly may not be ascertained, the benefit of screening by direct comparison of death rates from CAH in unscreened and screened populations cannot be readily demonstrated. Indeed, retrospective analysis of sudden infant death in the Czech Republic and Austria identified three genotype-proven cases of classic CAH among 242 samples screened (23). Moreover, males with salt-wasting CAH are more likely than females to suffer from delayed or incorrect diagnosis because there is no genital ambiguity to alert the clinician. Thus, a relative paucity of salt-wasting males is indirect evidence of unreported deaths from salt-wasting crises. In fact, females outnumber males in some (1, 24, 25) but not all (26) retrospective studies in which CAH was diagnosed clinically. In contrast, salt-wasting CAH patients ascertained through screening programs are equally likely to be male (19, 20, 22). The death rate in salt-wasting CAH without screening is between 4 and 10% (27, 28).

Affected infants ascertained through screening have less severe hyponatremia (mean serum sodium at diagnosis of 134 mM with screening, 124 mM without) (22, 29). Learning disabilities have been reported after salt-wasting crises (30); it is not known whether newborn screening reduces the frequency and severity of such abnormalities. Although salt-wasting males would seem to derive the greatest benefit from screening programs, the delay before correct sex assignment of severely virilized females is also markedly reduced (22, 31). Moreover, males with simple virilizing disease may otherwise not be diagnosed until rapid growth and accelerated skeletal maturation are detected later in childhood, at which time adult height may already be compromised. Cost-benefit analyses of newborn screening for CAH generally assume that the only adverse outcome of late diagnosis of CAH is death, particularly in males, and thus that the benefit is best quantified in life-years (infants saved by prompt diagnosis, multiplied by life expectancy). Calculations of costs per life-year saved are sensitive to the assumed death rate, and recent estimates have ranged widely from $20,000 (32) to $250,000–300,000 (33). It is conventionally assumed that screening for a particular disease is cost effective at less than $50,000 per life-year (32).

It is difficult to estimate the downstream costs of following up false-positive screens, which may entail a large amount of physician time for evaluation and counseling, plus nursing time and additional laboratory tests if cosyntropin testing is undertaken, Moreover, parents of infants with positive screens may suffer significant psychological distress at the prospect of their children having a potentially life-threatening chronic disease (34). These problems can be ameliorated by adopting screening methods with higher positive predictive values.

1.1 Values and preferences

In making this recommendation, the committee strongly believes that reducing morbidity and mortality from salt-wasting crises is a priority. This recommendation places a lower value in avoiding the incremental expenses of this screening program and subsequent medical care.

Recommendation

1.2 We recommend standardization of first-tier screening tests to a common technology with a single consistent set of norms stratified by gestational age (**1**|⊕⊕○○).

1.2 Evidence

First-tier screening tests

First-tier screens for CAH employ immunoassays to measure 17-OHP in dried blood spots on the same filter paper (Guthrie) cards as are used for other newborn screening tests (2–4). Both RIAs and ELISAs have been almost completely supplanted (9) (in at least 45 states and most European countries) by automated time-resolved dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA) (35).

In interpreting these tests, it must be remembered that 17-OHP levels are normally high at birth and decrease rapidly during the first few postnatal days. In contrast, 17-OHP levels increase with time in infants affected with CAH. Thus, diagnostic accuracy is poor in the first 2 d, which can be problematic if newborns are discharged early. Additionally, premature, sick, or stressed infants typically have higher levels of 17-OHP than term infants and generate many false positives unless higher cutoffs are used. There are no universally accepted standards for stratifying infants, but most U.S. laboratories use a series of birth weight-adjusted cutoffs (9, 36, 37). Specificity of

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newborn screening might be improved by using actual gestational age to stratify subjects, rather than birth weight, because 17-OHP levels are much better correlated with gestational age (38). Indeed, in The Netherlands and Switzerland, adopting gestational age criteria improved the positive predictive value of screening (29, 39). Finally, antenatal corticosteroid treatment (as used to induce lung maturation in fetuses at risk for premature birth) might reduce 17-OHP levels, but inconsistent effects have been observed in practice (40, 41). It is recommended that all such infants be retested after several days of life.

Second-tier screening tests

To obtain adequate sensitivity, the cutoff levels for 17-OHP are typically set low enough that approximately 1% of all tests are reported as positive. Despite the high accuracy of the screening test and given the low prevalence of CAH (about one in 10,000 births), only approximately one in every 100 neonates with a positive screening test will have CAH. Much of the expense of following up positive newborn screening tests could be avoided with a second level of more specific screening. Both biochemical and molecular genetic approaches have been proposed.

Biochemical second screens. Limitations of immunoassays for 17-OHP include true elevations in levels in premature, sick, or stressed infants and lack of specificity of some antibodies for 17-OHP. Immunoassay specificity can be increased by organic solvent extraction; this is currently mandated as a second screen in four states.

However, liquid chromatography followed by tandem mass spectrometry (LC-MS/MS) more effectively addresses many of these issues (42, 43), particularly when steroid ratios are measured. Implementation of this approach improved the positive predictive value of CAH screening in Minnesota from 0.8 to 7.6% during a 3-yr follow-up period (44). In Utah, the positive predictive value improved from 0.4 to 9.3% using similar methodology (45). A modified LC-MS/MS protocol using a ratio of the sum of 17-OHP and 21-deoxycortisol levels, divided by the cortisol level, had a positive predictive value of 100% when this ratio exceeded 0.53 when 1609 samples with a positive primary screen (of 242,500 samples screened by a German program) were tested prospectively (46). If these results can be replicated in other programs, this should become the method of choice for confirming positive screening results. Indeed, if throughput is improved, LC-MS/MS could be used as a primary screen for CAH (47), and problematic immunoassays might be eliminated completely.

Molecular genetic second screens. *CYP21A2* mutations can be detected in DNA extracted from the same dried blood spots that are used for hormonal screening. Because more than 90% of mutant alleles carry one of 10 mutations (deletions or gene conversions), patients carrying none of these mutations are unlikely to be affected. If at least one mutation is detected, the patient is evaluated further. Several studies of genotyping of samples from screening programs have suggested that this is a potentially useful adjunct to hormonal measurements (48–51), but no large-scale study of efficacy has been reported as a second-tier screen in actual use. Genotyping is more costly than LC-MS/MS on a per-sample basis. Additionally, it is focused on a single gene, *i.e. CYP21A2*, and will not be helpful in diagnosing other enzyme deficiencies causing CAH, as can be done with LC-MS/MS.

Recommendation

1.3 We recommend that infants with positive newborn screens for CAH be followed up according to specific regional protocols (**1**|⊕⊕○○).

1.3 Remarks

Cutoff values for screening tests must be empirically derived and vary by laboratory and assay. Whether and when to inform the infant's physician of record or a pediatric endocrinologist as well depends on the availability of subspecialists. Minimally elevated 17-OHP levels might warrant a second-tier screen from the same blood sample, whereas moderately elevated 17-OHP levels may be followed up with a repeat filter paper specimen. Higher values and signs of impending shock warrant urgent evaluation; in such cases, serum electrolytes and 17-OHP level (LC-MS/MS) are obtained. If the infant manifests clinical signs of adrenal insufficiency and/or abnormal electrolytes, a pediatric endocrinologist should be consulted for appropriate further evaluation and treatment.

The protocol for further evaluation will also depend on local and regional circumstances. Although the gold standard for hormonal diagnosis of CAH is a cosyntropin stimulation test (52), it may be difficult to perform on an urgent basis in many clinical settings. Treatment of infants with positive screens and obvious electrolyte abnormalities or circulatory instability should never be delayed for cosyntropin stimulation testing; in such infants, the adrenal cortex is highly stimulated anyway, and baseline steroids will be markedly elevated.

Extant norms are for tests employing a pharmacological dose of 0.125–0.25 mg cosyntropin (ACTH 1–24). In performing stimulation testing, it should be recognized that 17-OHP may be elevated in other enzymatic defects, particularly 11β-hydroxylase deficiency. One may more fully differentiate the various enzymatic defects potentially causing CAH by measuring 17-OHP, cortisol, deoxycorti-

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costerone, 11-deoxycortisol, 17-OH-pregnenolone, dehydroepiandrosterone (DHEA), and androstenedione after stimulation. Steroid profiling by LC-MS/MS of either serum or urine samples may ultimately supplant stimulation tests (53).

2.0 Prenatal treatment of CAH

Recommendations

2.1 We recommend that prenatal therapy continue to be regarded as experimental. Thus, we do not recommend specific treatment protocols.

2.2 We suggest that prenatal therapy be pursued through protocols approved by Institutional Review Boards at centers capable of collecting outcomes data on a sufficiently large number of patients so that risks and benefits of this treatment can be defined more precisely (**2**|⊕⊕○○).

2.1–2.2 Evidence

Basic considerations

The mechanism of dexamethasone's action in the fetus is incompletely understood. Nevertheless, suppression of fetal adrenal androgens in CAH is feasible by administering glucocorticoids (GCs) to the mother (54–56). Treatment aims to reduce female genital virilization, the need for reconstructive surgery, and the emotional distress associated with the birth of a child with ambiguous genitalia; prenatal treatment does not change the need for lifelong hormonal replacement therapy, the need for careful medical monitoring, or the risk of life-threatening salt-losing crises if therapy is interrupted. A single approach to prenatal treatment has been studied (57, 58), but optimal dosing and duration of treatment have not been determined. Fetal cortisol levels are low in very early gestation, rise during wk 8–12 while the external genitalia are differentiating (59), are only about 10% of maternal levels during midgestation (60, 61), and then increase during the third trimester. Thus, the constant dexamethasone dose currently used may result in GC levels that exceed typical midgestation physiological fetal GC levels by about 60-fold (62, 63).

CAH is autosomal recessive; if a woman has previously had a child with CAH and again becomes pregnant via the same partner, her fetus will have a one in four chance of having CAH. Because the period during which the genitalia of a female fetus may become virilized begins only 6 wk after conception, treatment must be instituted essentially as soon as the woman knows she is pregnant. Dexamethasone is used because it is not inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (64). Because treatment must be started at 6–7 wk gestation, and genetic diagnosis by chorionic villous biopsy cannot be done until 10–12 wk, all pregnancies at risk for CAH are treated, even though only one in four is affected. Furthermore, only half of the affected fetuses will be females; hence, treatment is potentially beneficial for only one in eight fetuses.

Obtaining fetal DNA at chorionic villous biopsy reduces the length of time between instituting treatment and obtaining a genetic diagnosis. Knowing the specific mutations carried by each parent substantially increases the efficiency and speed of genetic diagnosis. Fetal sex determination from fetal Y-chromosomal DNA in maternal blood (65, 66) has been used in conjunction with prenatal treatment of CAH (67, 68). Because early fetal sex determination can improve the probability of treating an affected female fetus from one in eight to one in four, when the technique becomes more consistently accurate in early gestation, it should be a required component of all prenatal treatment research protocols.

At least four factors should be considered in evaluating prenatal treatment of CAH: fetal GC physiology, safety to the mother, safety to the fetus, and efficacy. Because antenatally administered GCs are widely used to induce fetal lung development in the third trimester, many studies have addressed the effects of late-gestation, high-dose, short-term administration, but this may not be germane to prenatal treatment of CAH. Reduced late-term dosing of dexamethasone has been proposed (63, 69) and merits further study.

Efficacy

Prenatal administration of dexamethasone has been advocated for the sole purpose of ameliorating or eliminating genital virilization of affected females, reducing the need for genital reconstructive surgery and the psychological impact of virilization. It has been suggested that prenatal dexamethasone may reduce hypothetical androgenization of the fetal female brain, but such effects are difficult to measure and are not the subject of published studies.

Limited data are available concerning treatment outcomes. The evidence regarding fetal and maternal sequelae of prenatal dexamethasone treatment for fetuses at risk for CAH is of low or very low quality due to methodological limitations and small sample sizes (70, 272). In the largest single series (58), among 532 pregnancies assessed for carrying a fetus with CAH, prenatal treatment was initiated in 281. Among 105 with classic CAH (61 females, 44 males), dexamethasone was given throughout pregnancy to 49. Among 25 CAH-affected females receiving dexamethasone before the ninth week of pregnancy, 11 had normal female genitalia, 11 had minimal virilization (Prader stages 1–2), and three were virilized (Prader stage 3); the mean Prader score for this group was 1.0. Among

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24 female fetuses where treatment was begun after wk 9, the genitalia averaged a Prader score of 3.0. Those never treated were most virilized, averaging 3.75. The group first describing prenatal treatment has reported treating 253 pregnancies (71), indicating that "prenatal therapy is effective in significantly reducing or even eliminating virilization in CAH females" and that "the success rate is over 80%." However, these reports do not provide actual numbers describing their outcomes and did not include control groups of nontreated pregnancies. In a small, carefully done study, three of six female fetuses treated to term were unvirilized, two had mild virilization to Prader stage 2, and a poorly compliant mother had a girl with Prader 2–3 genitalia (72). Thus, the groups advocating and performing prenatal treatment appear to agree that it is effective in reducing and often eliminating virilization of female fetal genitalia and that the success rate is about 80–85%.

Maternal safety

Among 118 women treated to term who responded to a mailed questionnaire, the mean pregnancy-associated weight gain was 7.1 lbs (3.2 kg) greater than that experienced by untreated women ($P < 0.005$); these women also reported increased striae ($P = 0.01$) and increased edema ($P = 0.02$) but no reported increase in hypertension or gestational diabetes (58). A review lacking a control group indicated that 9–30% of treated women complained of mild gastric distress, weight gain, mood swings, pedal edema, and mild hypertension and that only 1.5% of 253 treated women had serious complications including striae, large weight gain, hypertension, preeclampsia, and gestational diabetes (57). A carefully controlled study of 44 women receiving prenatal dexamethasone (only six to term) found increased weight gain in mothers treated during the first trimester, but this difference was absent at term. There were no differences in maternal blood pressure, glycosuria, proteinuria, length of gestation, or placental weight. However, in response to a questionnaire, compared with untreated controls, treated women reported increased appetite ($P < 0.01$), rapid weight gain ($P < 0.02$), and edema ($P = 0.04$), and 30 of the 44 women indicated they would decline prenatal treatment of a subsequent pregnancy (72). Other uncontrolled reports document Cushingoid effects in small numbers of treated women (73). Thus, multiple studies indicate that prenatal treatment is associated with modest but manageable maternal complications that do not appear to pose a major risk to the mother.

Fetal safety

Many reports of teratogenic effects, especially orofacial clefts, produced by high doses of dexamethasone administered to pregnant animals (74–76) and in human patients (77–79) led the U.S. Food and Drug Administration to classify dexamethasone as a category B drug, whose safety in pregnancy is not established. Prescription of dexamethasone for prenatal treatment of CAH is an off-label use in the United States and European Union. No teratogenic effects have been identified with high-dose GCs administered during gestation; however, these studies concerned steroids that are inactivated by placental 11β-HSD2 and as such do not affect the fetus (80, 81). A case-control study of 662 infants with orofacial clefts and 734 controls found higher incidences of isolated cleft lip (odds ratio 4.3) or cleft palate (odds ratio 5.3) among mothers who used GCs "during the 4-month periconceptual period" (82). A multicenter case control study by the same group surveying GC exposure among 1141 cases of cleft lip (with or without cleft palate), 628 with cleft palate, and 4143 controls found a lower risk (odds ratio = 1.7; 95% confidence interval = 1.1–2.6). The data suggested greatest risk for exposure between 1–8 weeks, but the numbers were small (odds ratio = 7.3; 95% confidence interval = 1.8–29.4) (83).

Because newborn birth weight correlates with adult incidences of ischemic heart disease and hypertension (84, 85) and because moderately low-dose dexamethasone (100 μg/kg) reduced birth weight and increased blood pressure in rats (86), concern was raised about the effects of prenatal dexamethasone treatment in CAH (87–89). Prenatal dexamethasone alters postnatal renal structure and function and produces hypertension in rodents (90, 91). One year after prenatal exposure of nonhuman primates to 120 μg/kg dexamethasone, there were reduced pancreatic β-cell numbers, impaired glucose tolerance, increased systolic and diastolic blood pressure, and reduced postnatal growth despite normal birth weight (92). Follow-up reports of prenatally treated children have reported birth weights in the normal range (56, 57, 71, 72) but are nevertheless reduced by about 0.4–0.6 kg in the largest studies (58). The magnitude of this change in birth weight is equivalent to or greater than that seen with maternal cigarette smoking (93). The long-term significance of this reduction in mean birth weight remains of concern.

It is uncertain whether GCs are required for normal human development. A child born with complete generalized GC resistance had no major organ defects (94). Clearly, high doses of GCs exert negative effects in fetal animals (95, 96). Dexamethasone administered to pregnant sheep during early gestation in doses similar to those used in CAH prenatal therapy altered fetal adrenal and placental steroidogenesis (97). Betamethasone treatment in mid to late gestation reduced brain weight (98, 99) and

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neuronal myelinization (100) in fetal sheep. High doses of maternally administered dexamethasone also disrupted development of hippocampal neurons in late-term fetal rhesus monkeys (101). Whether these observations are relevant to reports of mild emotional and cognitive disturbances in prenatally treated children is not clear. Questionnaires administered to dexamethasone-treated children showed more shyness and inhibition (102). A questionnaire study of 174 children prenatally treated and 313 untreated control children found no differences between treated and untreated groups with respect to nine social/developmental scales (103). A small but rigorous study, using a standardized treatment protocol, questionnaires, and standardized neuropsychological tests administered by a clinical psychologist, compared prenatally treated children and a control group matched for age and sex. No differences were found in intelligence, handedness, or long-term memory. However, CAH-unaffected children prenatally treated short term had poorer verbal working memory, rated lower on self-perception of scholastic competence (both $P = 0.003$), and had increased self-rated social anxiety ($P = 0.026$) (104). The parents of the prenatally treated children described them as being more sociable than controls ($P = 0.042$); there were no differences in psychopathology, behavioral problems, or adaptive functioning (105). Systematic review and metaanalysis of these publications have not detected significant differences in behavior or temperament (70), and only a single small study indicates a modest but measurable effect of dexamethasone on postnatal cognitive function (104).

Given the small number of potentially affected patients being treated, clinical research of prenatal treatment should be conducted only in centers of excellence coordinating treatment protocols in multicenter studies with standardized registries. Such approaches may provide robust data to guide practice sooner than individual center studies testing idiosyncratic protocols with limited statistical power. Although these will have less protection against bias, centers that have already treated many pregnancies should perform and publish studies of their experience with emphasis on the physical and psychological outcomes in childhood and adolescence, distinguishing between patients treated short term and long term.

2.1–2.2 Values and preferences

The prenatal treatment of CAH remains controversial and poses unresolved ethical questions (62, 87, 89, 106–111). The concern is treating seven unaffected and/or male fetuses to treat one affected female in the context of inadequate data regarding the long-term risks of this therapy. Prenatal treatment of CAH is directed toward reducing the need for surgery, rather than toward preserving life or intellectual capacity. Therefore, in validating earlier expert opinion, this Task Force placed a higher value on preventing unnecessary prenatal exposure of mother and fetus to dexamethasone and avoiding potential harms associated with this exposure and a relatively lower value on minimizing the emotional toll of ambiguous genitalia on parents and patients.

3.0 Diagnosis of NCCAH/CAH after infancy

Recommendations

3.1 We recommend obtaining an early morning baseline serum 17-OHP in symptomatic individuals (**1**|⊕⊕○○).

3.2 We recommend obtaining a complete adrenocortical profile after a cosyntropin stimulation test to differentiate 21-hydroxylase deficiency from other enzyme defects and to make the diagnosis in borderline cases (**1**|⊕⊕○○).

3.3 We suggest genotyping only when results of the adrenocortical profile after a cosyntropin stimulation test are equivocal or for purposes of genetic counseling (**2**|⊕○○○).

3.1–3.3 Evidence

The diagnosis of 21-hydroxylase deficiency is based on measuring 17-OHP, the enzyme's principal substrate, and excluding 11-hydroxylase and P450 oxidoreductase deficiencies, in which 17-OHP may also be elevated. A sample diagnostic strategy is portrayed in Fig. 2.

Other steroids whose levels are usually elevated include 21-deoxycortisol, androstenedione, and testosterone. Elevated plasma renin activity (PRA) and a reduced ratio of aldosterone to PRA indicate impaired aldosterone synthesis and can differentiate salt wasters from simple virilizers (112) after the newborn period.

The severity of hormonal abnormalities depends on the degree of the enzymatic impairment, which depends on the genotype. A genetic test cannot detect salt wasting; this requires careful clinical evaluation. For example, genotyping may reveal the *IVS2* mutation, which is seen in both salt-wasters and non-salt-wasters (15, 113, 114). Compound heterozygotes for two different *CYP21A2* mutations usually have a phenotype compatible with the milder mutation. Heterozygotes have slightly elevated 17-OHP levels after ACTH stimulation, but there is overlap with unaffected subjects (115). Other analytes have been used as markers of heterozygosity (116, 117), but genotyping is a usually superior method of heterozygote detection.

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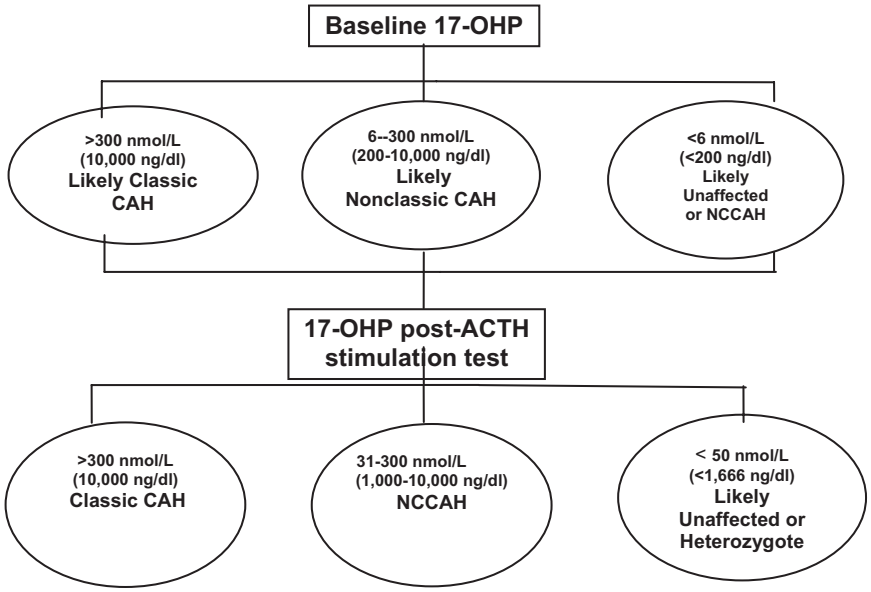

FIG. 2. Diagnosis of CAH after infancy. Reference standards for hormonal diagnosis derived from Refs. 115, 218, 219, and 273. Note that randomly measured 17-OHP levels can be normal in NCCAH; hence, a screening 17-OHP level should be measured in the early morning (before 0800 h). Steroid measurements may differ with the assay employed. Classic CAH includes both salt-wasting and simple virilizing forms of 21-hydroxylase deficiency.

4.0 Medical treatment of CAH in growing patients

Recommendations

Glucocorticoids

4.1 We recommend maintenance therapy with hydrocortisone (HC) tablets in growing patients with classic CAH (**1**|⊕⊕⊕○).

4.2 We recommend against the use of oral HC suspension and against the chronic use of long-acting potent GCs in growing patients (**1**|⊕⊕○○).

4.3 We recommend monitoring patients for signs of GC excess as well as for signs of inadequate androgen suppression (**1**|⊕⊕○○).

Mineralocorticoids (MCs)

4.4 We recommend that all patients with classic CAH be treated with fludrocortisone and sodium chloride supplements in the newborn period and early infancy (**1**|⊕⊕○○).

4.1–4.4 Evidence

The goal of therapy is to reduce excessive androgen secretion by replacing the deficient hormones. Proper treatment with GCs prevents adrenal crisis and virilization, allowing normal growth and development. Clinical management of classic CAH is a difficult balance between hyperandrogenism and hypercortisolism. Undertreatment carries the risk of adrenal crisis and allows increased adrenal androgen production, with accelerated bone age and loss of growth potential; overtreatment may suppress growth, increase blood pressure, and cause iatrogenic Cushing's syndrome.

For initial reduction of markedly elevated adrenal hormone levels in infancy, one may exceed the recommended GC doses, but it is important to rapidly reduce the dose when target steroid levels are achieved. Frequent reassessment is needed in infancy. Attempts to completely normalize 17-OHP levels typically result in overtreatment. During childhood, the preferred GC is HC because its short half-life minimizes the adverse side effects of more potent longer-acting GCs, especially growth suppression (118). In one trial, the estimated growth-suppressive effect of prednisolone was about 15-fold more potent than HC (119); dexamethasone is 70- to 80-fold more potent (120). HC suspension and HC tablets are not bioequivalent, and HC oral suspension may be inadequate to control CAH in children (121) due to uneven distribution of the drug in liquid. Good control can be achieved by orally administering crushed HC tablets mixed with a small volume of liquid immediately before administration. Insufficient data exist to recommend higher morning or evening doses (122). When doses exceed 20 mg/m^2 · d in infants and 15–17 mg/m^2 · d in adolescents, there is loss of height SD score (SDS) and shorter adult height SDS (123–127). Table 1 provides suggested dosing guidelines. Thus, although prednisolone and dexamethasone treatment are effective in suppressing adrenal androgens in children with CAH, these more potent drugs are more likely to impede statural growth and cannot be routinely recommended.

During puberty, despite adequate replacement therapy and compliance, control may be suboptimal because of

TABLE 1. Maintenance therapy in growing CAH patients

Drugs	Total dose	Daily distribution
GCs: HC tablets	10–15 mg/m^2 · d	3 times/d
MCs: fludrocortisone tablets	0.05–0.2 mg/d	1–2 times/d
Sodium chloride supplements	1–2 g/d (17–34 mEq/d) in infancy	Divided in several feedings

The doses and schedules are meant as examples and should not be construed as a restrictive menu of choices for the individual patient.

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TABLE 2. Maintenance therapy suggested in fully grown patients

Type of long-acting GC	Suggested dose (mg/d)	Daily doses
HC	15–25	2–3
Prednisone	5–7.5	2
Prednisolone[a]	4–6	2
Dexamethasone[a]	0.25–0.5	1
Fludrocortisone	0.05–0.2	1

[a] Suspension or elixir may permit better dose titration for these drugs.

increased cortisol clearance (128). Adult height of CAH patients correlates negatively with the dose of GC administered in early puberty; patients treated with less than 20 mg HC/m^2 · d at start of puberty are significantly taller than those who were given higher HC doses. Therefore, as with younger patients, it is important during puberty to treat with the lowest possible dose (118).

At or near completion of linear growth, long-acting GCs may be used (see Table 2), although HC remains a treatment option. Prednisolone suspension or dexamethasone elixir can be used to titrate the dose more finely than with tablets.

Infants with salt-wasting 21-hydroxylase deficiency require MCs in addition to GC treatment as well as supplemental sodium chloride. The requirement for sodium in normally growing infants is approximately 1 mmol/kg · d, the amount provided by human milk. However, in salt-wasting CAH patients, the sodium content of breast milk or infant formulas is insufficient, and sodium chloride supplements are necessary (129).

Although the aldosterone biosynthetic defect is clinically apparent only in the salt-wasting form, subclinical aldosterone deficiency is present in all forms of 21-hydroxylase deficiency (112, 130, 275) and can be best evaluated by the aldosterone to PRA ratio. The latter decreases with increasing phenotypic severity, clearly demonstrating a spectrum of salt loss in the various forms of 21-hydroxylase deficiency (112). Consequently, all patients with elevated PRA or aldosterone to PRA ratio benefit from fludrocortisone therapy and adequate dietary sodium. Maintenance of sodium balance reduces vasopressin and ACTH levels, contributing to lower GC doses, leading to better auxological outcomes (108, 123, 131).

Sensitivity to MCs may vary over time, and recovery from salt wasting has been described in some patients, most probably secondary to extraadrenal 21-hydroxylation (132, 133). Therefore, the need for continuing MCs should be reassessed periodically based on blood pressure, PRA, and the aldosterone to PRA ratio. It is particularly important to monitor blood pressure in infants who are often initially treated with high doses of MC due to immature renal tubular capacity to reabsorb sodium.

4.1–4.4 Values and preferences

The proposed GC choice places higher value on reducing the negative effects on growing children than on convenience and compliance.

Recommendations

Stress dosing

4.5 We recommend increasing the GC dosage of CAH patients in situations such as febrile illness (>38.5 C), gastroenteritis with dehydration, surgery accompanied by general anesthesia, and major trauma (**1**|⊕⊕○○).

4.6 We recommend against the use of increased GC doses in mental and emotional stress and minor illness and before physical exercise (**1**|⊕○○○).

4.7 We recommend against the use of stress doses of GC in patients with NCCAH unless their adrenal function is suboptimal or iatrogenically suppressed (**1**|⊕○○○).

4.8 We suggest that patients who require treatment always wear or carry medical identification indicating that they have adrenal insufficiency (**2**|⊕○○○).

4.5–4.8 Evidence

Patients with severe forms of 21-hydroxylase deficiency are unable to produce a sufficient cortisol response to physical stress, such as febrile illness, gastroenteritis with dehydration, surgery, or trauma, and therefore require increased doses of GC during such episodes (Table 3). When pharmacological doses of HC are given, MCs are not needed because HC can activate MC receptors. Maintenance doses should be resumed when the patient is stable. Patients should avoid fasting during acute illnesses; glucose and electrolyte supplementation should be given to young children due to risk of hypoglycemia and electrolyte imbalance.

Exercise and psychological stresses (*e.g.* anxiety and examinations) (134) do not require increased GC dosing (135).

Recommendations

Monitoring therapy in growing children

4.9 We recommend monitoring treatment by consistently timed hormone measurements (**1**|⊕○○○).

4.10 We recommend that endogenous adrenal steroid secretion not be completely suppressed to avoid adverse effects of overtreatment (**1**|⊕⊕○○).

TABLE 3. Suggested stress doses of GC

Patient age	Initial parenteral HC dose (mg)
Infants and preschool children	25
School-age children	50
Adults	100

Successive iv HC doses are given as three to four times maintenance doses per day, divided every 6 h.

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4.11 We suggest regular monitoring of height, weight, and physical examination; annual bone age assessment is suggested after age 2 yr (**2**|⊕○○○).

4.9–4.11 Evidence

Monitoring treatment is difficult in CAH. Normal growth and growth velocity are important variables in children. Either a reduced or an accelerated height velocity, signs of virilization, and delayed or premature bone maturation usually occur after protracted under- or overtreatment. Laboratory data should indicate the need for dose adjustment before growth and physical changes occur. 17-OHP, androstenedione, and testosterone are the best indicators of the adequacy of GC treatment. Steroid measurements can be performed in blood, saliva (136, 137), urine (138), or dried filter paper blood samples (139, 140). Assays of sufficient sensitivity such as immunoassays after extraction and chromatography, or LC/MS-MS, should be used in conjunction with appropriate reference data (42, 141). Normal levels of 17-OHP and the other steroids are not a treatment goal but instead indicate overtreatment. ACTH measurements are not useful for a diagnostic or therapeutic profile in CAH patients. Acceptably treated CAH patients generally have mildly elevated steroid levels when measured in a consistent manner, and dose adjustments should be made in the context of the overall clinical picture and not solely based on a single 17-OHP measurement.

5.0 Treatment of NCCAH

Recommendations

5.1 We suggest treating NCCAH children with inappropriately early onset and rapid progression of pubarche or bone age, and adolescent patients with overt virilization (**2**|⊕⊕○○).

5.2 We recommend against treatment in asymptomatic individuals with NCCAH (**1**|⊕⊕○○).

5.3 We suggest that previously treated NCCAH patients be given the option of discontinuing therapy when symptoms resolve (**2**|⊕⊕○○).

5.1–5.3 Evidence

Our unsystematic clinical observations suggest that children with inappropriately early onset of body hair and odor should be treated only when bone maturation is sufficiently accelerated to adversely affect height. In the presence of premature pubarche without advanced bone age, treatment can be withheld during careful monitoring. In adolescents with irregular menses and acne, symptoms are usually reversed within 3 months of GC treatment, whereas remission of hirsutism is more difficult to achieve with GC monotherapy. As in other androgenic disorders, treatment of hirsutism may be best served by the addition of an oral contraceptive and/or antiandrogens (142, 143).

6.0 Complications of CAH

Recommendations

6.1 We recommend close monitoring for iatrogenic Cushing's syndrome in all GC-treated patients (**1**|⊕⊕○○).

6.2 We suggest against the routine evaluation of bone mineral density (BMD) in children (**2**|⊕○○○).

6.3 We suggest that adrenal imaging be reserved for those patients who have an atypical clinical or biochemical course (**2**|⊕○○○).

6.1–6.3 Evidence

Prolonged steroid therapy may reduce BMD. However, in CAH children and adolescents on standard GC therapy (10–20 mg/m^2), there is no evidence of decreased BMD assessed by dual-energy x-ray absorptiometry and normalized for height, irrespective of duration of treatment, type of GC used, and 17-OHP or androgen levels (144–147). Longitudinal follow-up studies of BMD from childhood to adulthood would be useful. At present, the standard of care for good bone health includes age-appropriate vitamin D and calcium intake along with weight-bearing exercise.

Adrenal masses affect 1–4% of normal men and women (148). Their prevalence in autopsy samples increases with age, being 0.2% in young adults and 7% in subjects older than 70 yr (149). A high prevalence of benign adrenal masses has been observed by computed tomography imaging in adults with CAH, especially among those on inadequate GC therapy (150). Adrenal carcinomas have rarely been reported in adults (151) and in only two pediatric patients with CAH (152, 153). Insufficient data exist to recommend routine screening for adrenal masses. If an adrenal incidentaloma is discovered in a patient not known to have CAH, the various forms of CAH should be excluded by appropriate testing (152).

The prevalence of testicular adrenal rests in boys with classic CAH aged 2–18 yr varies from 21–28% (154–156); there have been no such studies in NCCAH males. These so-called testicular adrenal rest tumors are benign, often related to suboptimal therapy, and usually decrease in size after optimization of GC therapy (157). Testicular masses in boys with classic CAH are usually bilateral and smaller than 2 cm in diameter and therefore not palpable but detectable by ultrasound (US) (154–156).

Irregular menstrual cycles are common in females with inadequately treated classic CAH (158, 159). However, in a controlled study of 62 adult women with CAH (160), there was no difference in the prevalence of irregular menses between treated CAH and control women. Menstrual

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irregularity is typically one of the presenting signs (161, 162) in NCCAH. A polycystic ovary syndrome type of functional ovarian hyperandrogenism may cause irregular menses in women with well-controlled CAH (163, 164); the hyperandrogenism and menstrual irregularity of such individuals benefits from additional therapy with second- or third-generation oral contraceptives. Studies in a limited number of adolescent CAH patients showed a prevalence of polycystic ovaries on US corresponding to that in the general population (165, 166). If one examines unselected populations of hyperandrogenic, hirsute women, or patients in fertility clinics, the incidence of NCCAH is 2–4% (167–169).

Children with CAH have a higher body mass index than do controls due to increased fat mass (170). Studies in pediatric patients showed that approximately half are overweight, and 16–25% are obese (170–172). Hypertension is more prevalent in children with classic CAH than in the general population, and systolic blood pressure was related to body mass index independent of GC or MC therapy (173, 174). In a small group of prepubertal children with classic CAH, serum leptin and insulin concentrations were significantly higher than those of healthy counterparts. Whereas subtle insulin resistance can be detected in untreated NCCAH (274), frankly impaired glucose tolerance is uncommon. Oral glucose tolerance was normal in nine of 10 girls with classic CAH aged 8–20 yr (165). Inconsistent data have been reported on triglyceride levels, with one study reporting higher levels in a group of prepubertal patients on GC treatment compared with age-matched controls (175) and another showing a lipid profile in CAH children similar to that of controls (176). These differences probably reflect small sample sizes in both studies.

In view of increased body fat and potential metabolic consequences, we suggest that lifestyle counseling to counteract these trends begin early.

7.0 Feminizing surgery

Recommendation

7.1 We suggest that for severely virilized (Prader stage ≥ 3) females, clitoral and perineal reconstruction be considered in infancy and performed by an experienced surgeon in a center with similarly experienced pediatric endocrinologists, mental health professionals, and social work services (**2**|⊕⊕○○).

7.1 Evidence

For goals and functional outcomes of genital surgery, see section 10.0, *Mental health*. There are no randomized controlled studies of either the best age or the best methods for feminizing surgery. The results must be evaluated at adult ages, often 20 yr or more after the initial surgery, and during that time methods may have changed several times.

The timing for vaginoplasty is debated; however, we suggest that in patients with a low vaginal confluence, complete repair including vaginoplasty, perineal reconstruction, and clitoroplasty (if necessary) be done simultaneously at an early age. For individuals with higher vaginal confluence, the timing is less certain. The implied surgical advantage of delayed reconstruction is that the risk of vaginal stenosis and the need for subsequent dilation is diminished. In infants with severe virilization where clitoroplasty is being considered, the advantages of early complete reconstruction are that the phallic skin can also be used as part of the vaginal reconstruction and gives the surgeon much more flexibility. In the neonatal period, the recent exposure to placental estrogens leads to more elastic vaginal tissue, facilitating vaginal reconstruction (177).

If surgery is deferred, vaginoplasty and/or clitoroplasty may be performed in adolescence. Systematic long-term evaluation is lacking for both early and late surgery, for which significant postoperative complications may occur, such as urethra-vaginal fistulae and vaginal stenosis. There are no data comparing psychosexual health in girls and women who have undergone early and late surgery. Parents should be provided with balanced information about timing, risks and benefits of surgery; they should be informed that deferring surgery is an option. It is important that the long-term prognosis for sexual and reproductive function be discussed. There is no evidence at this time that either early or late surgery better preserves sexual function.

7.1 Values and preferences

Presumed values in seeking early surgery are reducing parental anxiety and easing acceptance of the child's congenital anomaly, avoiding stigmatization of a girl with masculinized genitals, and avoiding the psychological trauma of genital surgery during adolescence. Presumed values of late surgery are patient autonomy regarding surgery that may damage sexual function.

7.1 Remarks

Genital reconstructive surgery requires both surgical experience and the endocrine, anesthesia, nursing, and psychosocial support that is found only in centers that do this procedure regularly.

Recommendation

7.2 We suggest neurovascular-sparing clitoroplasty and vaginoplasty using total or partial urogenital mobilization (**2**|⊕○○○).

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7.2 Evidence

The description of total urogenital mobilization by Peña (178) signaled a significant advance in the surgical management of CAH. The basic technique involves a 360° mobilization of the entire urogenital sinus, which is then brought to the perineum. In partial urogenital mobilization, dissection is avoided superior to the urethra under the pubic bone, a nerve-rich zone that contains the sphincteric musculature necessary for urinary continence. Urinary incontinence and vaginal stenosis requiring dilation or reoperation remain a postoperative concern but have not been reported by either Peña (179) or Rink (180–182). Long-term follow-up is necessary to confirm these findings. This recommendation is based on the poor results of other forms of vaginoplasty (147, 183), including flap vaginoplasty for severe CAH and vaginal pull-through separating the urethra and vaginal components, and is consistent with the consensus statement on 21-hydroxylase deficiency from the Pediatric Endocrine Society (formerly known as Lawson Wilkins Pediatric Endocrine Society) and the European Society for Pediatric Endocrinology (107).

Recommendation

7.3 We suggest continued long-term outcome studies of early surgery.

7.3 Evidence

In contrast to other significant congenital abnormalities of the genitourinary system (bladder exstrophy, prune belly syndrome, and posterior urethral valves), the incidence of urogenital sinus anomalies associated with CAH has not decreased. Thus, there is a continuing need to derive evidence-based guidelines for surgical treatment of CAH. A metaanalysis and systematic review of the surgical treatment of CAH in 5 yr is a reasonable goal.

7.3 Values and preferences

The majority of women with CAH surveyed favored genital surgery before adolescence (184, 185). The Task Force shares the stated preference of the majority of patients and places a high value on the outcomes of early complete repair done by surgeons experienced with either total or partial urogenital mobilization, *e.g.* reduced need for dilation in adolescence or adulthood and maintaining normal perineal and clitoral sensation.

7.3 Remarks

The decision of whether or when to perform surgery is often difficult. The pediatric endocrinologist, surgeon, social worker, and mental health professionals should meet as a team to discuss various options with the family and continue to provide support. Patient and parent support groups may also be enlisted to provide guidance to the family and relate experiences of those who have recently made such decisions.

8.0 Experimental therapies

Childhood experimental therapies to enhance growth

Recommendations

8.1.1 We suggest that children with CAH who have a predicted height SD of −2.25 or below be considered for experimental treatment in appropriately controlled trials (**2**|⊕◯◯◯).

8.1.2 We recommend against use of experimental treatment approaches outside of formally approved clinical trials (**1**|⊕⊕◯◯).

8.1.3 We suggest further prospective, randomized, and carefully controlled studies to determine whether the use of growth-promoting drugs increases adult height in patients with CAH (**2**|⊕◯◯◯).

8.1.1–8.1.3 Evidence

The goal of many new treatment approaches is to normalize growth and development in children with CAH. The adult short stature of many CAH patients may be caused by hypercortisolism, hyperandrogenism, or both. Retrospective studies show that adult height is relatively independent of adrenal androgen levels in treated patients (186–188). In a study of 341 treated patients with classic CAH, 124 were examined at adult height. Males and females were 10 and 8 cm shorter than expected, respectively (189). A metaanalysis of data from 18 centers worldwide showed that the mean adult height of patients with classic CAH was 1.37 SD (10 cm) below the mean, and patients diagnosed before 1 yr of age had increased adult height outcomes (0.54 SD) (190). In nonsystematic reviews, patients who were diagnosed late or were exposed to GC doses higher than 15 $mg/m^2 \cdot d$ had diminished height (191, 192). Overtreatment during infancy (126, 193) or treatment with long-acting, high-potency GCs may also reduce height (118). The pubertal growth spurt is attenuated in CAH adolescents (118). Despite these concerns, height approximating target height has been reported in patients with strict adherence to thrice-daily medication and monitoring every 3 months (118, 194, 195). Thus, vigilance during the first 2 yr of life and during puberty is important in optimizing height.

A systematic review and metaanalysis of adult height in patients with classic CAH diagnosed before age 5 yr was prepared in conjunction with these guidelines (131). Of 1016 published reports, only 35 met eligibility criteria for

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inclusion in the analysis. All were observational studies with methodological limitations, graded very low-quality evidence. Most patients were diagnosed before the era of newborn screening, fewer than half reported a mean age of diagnosis under 1 yr, and most did not give details of GC doses. The pooled data indicated a corrected adult height SDS of −1.05. Subgroup analysis revealed that the addition of MC treatment was associated with increased height outcome. Age at diagnosis, sex, type or dose of steroid, and age of onset of puberty did not significantly influence adult height; however, these subgroup analyses were inconclusive.

Patients with NCCAH can also have compromised adult height, but height deficit is less severe than with classic CAH. However, there is limited evidence that initiation of GC treatment before puberty might improve adult height (187, 196). Similarly, there are limited studies evaluating drugs that enhance growth in children with classic CAH.

A four-drug regimen of the antiandrogen flutamide, the aromatase inhibitor testolactone, reduced HC (8 mg/$m^2 \cdot d$), and fludrocortisone decreased growth rate, weight velocity, and bone maturation as compared with conventional treatment with HC and fludrocortisone in a crossover study of 12 children (197). In a 2-yr randomized parallel study of 28 children, patients receiving the experimental four-drug regimen had normal linear growth and bone maturation, despite elevated adrenal androgens (198). Long-term safety data are unknown; blood chemistries and liver function must be carefully monitored during treatment with synthetic antiandrogens.

A 1- to 2-yr nonrandomized study of children with CAH showed improved growth rate and height z score for bone age for GH used alone (n = 12) or in combination with GnRH agonist (GnRHa) (n = 8; $P < 0.0001$) (199). A combined regimen of GH and GnRHa was administered to 14 patients selected for a predicted height of more than 1 SD below target height. Patients treated with this regimen plus conventional therapy for approximately 4 yr had improved adult height (+1.1 SD) (200). Adult height of the patients treated with this combined regimen for approximately 4 yr was greater than the adult height of matched historical CAH controls treated with conventional therapy alone (SD −0.4 *vs.* −1.4, $P = 0.01$). GnRHa treatment increases adult height in CAH children who develop central precocious puberty (201). No randomized study has investigated the effect of GnRHa alone on adult height in children with CAH and normally timed puberty.

Well-designed, large, randomized, controlled studies of experimental drugs aimed at improving adult height of children with CAH are needed. Present evidence is insufficient to warrant recommending use of sex steroid blockade, GH, or GnRHa in children with CAH outside of controlled Institution Review Board-approved trials. Normal adult height can be achieved in CAH with judicious use of standard GC and MC therapies, and height-enhancing drugs are not recommended for individuals whose height is, or is expected to be, more than −2.25 SD.

See links to *Resources for Clinical Trials on CAH* in Supplemental Material, Appendix 1.

8.1.1–8.1.3 Values and preferences

In recommending further research on experimental therapies in children with low predicted adult height, the Task Force placed high value on reducing potential psychosocial consequences of extreme short stature.

Adrenalectomy

Recommendation

8.2 We suggest that bilateral adrenalectomy be considered only in select cases that have failed medical therapy, especially in rare cases of adult females with salt-wasting CAH and infertility. Risk for noncompliance must be considered before surgery (**2**|⊕○○○).

8.2 Evidence

Bilateral adrenalectomy for CAH is controversial. Bilateral adrenalectomy reduces the risk of virilization in females and allows for treatment with lower GC doses. Objections to adrenalectomy are based on surgical risk, possible increased risk of adrenal crisis due to loss of protective residual adrenal function, and possible loss of hormones that may have beneficial effects such as epinephrine and DHEA.

Van Wyk and Ritzen (202) reported follow-up of 18 patients with CAH (14 salt-wasting, two simple virilizing, one nonclassic, and two 11-hydroxylase deficiency) from 11 centers who underwent bilateral adrenalectomy (13 laparoscopic and five open flank). Three patients were children (aged 1–8 yr) who had prophylactic adrenalectomy as part of a research protocol, and 15 patients were difficult to manage with conventional therapy. During approximately 5 yr of follow-up, five patients had one or more adrenal crises and two of the younger patients experienced severe hypoglycemia with illness. All patients reported subjective benefits after surgery, including the need for less frequent monitoring, weight loss, and fewer signs and symptoms of androgen excess. Eight patients had elevated steroid precursors postoperatively while on reduced HC dose, presumably from adrenal rest tissue activation, which required increased HC doses. However, GC doses were lower after than before adrenalectomy.

Five adult (aged 21–37 yr) female patients with salt-wasting CAH underwent bilateral adrenalectomy with mean follow-up of 4.2 yr (203). Two patients underwent adrenalectomy for infertility and became pregnant within

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2 yr. Three patients underwent adrenalectomy for unsuppressible hyperandrogenism and worsening obesity. Weight loss was achieved; however, all three patients experienced pigmentation and adrenal crises during follow-up.

Laparoscopic bilateral adrenalectomy was performed in two women (aged 22 and 28 yr) with classic salt-wasting CAH for difficult-to-suppress androgens, with amenorrhea, hirsutism, and acne (204). Weight loss and regular menstruation followed in both patients, and one had a successful pregnancy 3 yr postoperatively. One patient had mildly elevated adrenal steroid precursors, likely due to adrenal rest tissue.

Individuals with a history of noncompliance are poor candidates for adrenalectomy because postoperative noncompliance in an adrenalectomized patient could be fatal.

If fertility is desired and adrenalectomy is not an option, hyperandrogenism can be overridden by clomiphene or GnRH ovarian stimulation.

8.2 Remarks

This recommendation requires a surgeon experienced in bilateral adrenalectomy. The lifetime risk of adrenal crisis must be thoroughly evaluated before considering this option.

Physiological cortisol replacement

Recommendation

8.3 We suggest the development of new treatment approaches that minimize daily GC exposure and aim to achieve physiological cortisol replacement.

8.3 Evidence

Existing GC therapy is nonphysiological and may contribute to adverse outcomes. Normal adrenocortical secretion has a circadian rhythm with levels low at onset of sleep, rising between 0200 and 0400 h, peaking in the early morning at approximately 0800 h, and then declining throughout the day (205, 206). Programmed infusion of HC delivered in a circadian fashion to poorly controlled CAH patients resulted in nearly normal ACTH and 17-OHP (207, 208). A modified-release oral form of HC is being developed (209). Further studies are needed to determine whether more physiological cortisol replacement could improve long-term clinical outcome.

Epinephrine deficiency

Recommendation

8.4 We suggest additional research concerning epinephrine deficiency in the stress response.

8.4 Evidence

Patients with classic CAH have adrenomedullary insufficiency because GCs play essential roles in the development and regulation of the adrenal medulla (198, 210). Combined cortisol and epinephrine deficiency results in glucose, insulin, and leptin dysregulation, shown during short-term high-intensity exercise (211, 212) and long-term moderate-intensity exercise (213). The clinical implications of epinephrine deficiency are not fully known, but it likely plays a role in the risk for hypoglycemia during febrile illnesses, especially in young children. Chronic adrenomedullary hypofunction also may play a role in the development of insulin resistance (214). Epinephrine replacement or supplementation has not been studied.

Preclinical research

Recommendation

8.5 We suggest continued research concerning novel therapies.

8.5 Evidence

CRH antagonists have been investigated in animals for potential use in psychiatric disorders (215). Increased secretion of hypothalamic CRH is expected in CAH. CRH antagonists may permit lower-dose GC replacement in the treatment of CAH (216). ACTH antagonists could have a similar effect. Drugs that block specific steroidogenic steps might also normalize adrenal androgen production without supraphysiological GC doses.

Gene therapy temporarily restored adrenal steroidogenesis in 21-hydroxylase-deficient mice (217). Patients with CAH have the ability to regulate cortisol normally; thus, altering cells to become cortisol producing represents a potential cure. The ability to correct the genetic mutations causing CAH by applying gene therapy to an individual's own stem cells would theoretically cure CAH and avoid the need for immune-suppressant therapy. However, in light of the current practical barriers to gene therapy, risks associated with viral gene therapy vectors, the need for high levels of expression of enzyme activity within the adrenal cortex, and the availability of effective medical therapy for this condition, gene therapy is unlikely to be a realistic option for this disorder for decades to come.

Future studies

Recommendation

8.6 We suggest that further study of alternative treatment approaches consider growth, metabolic, reproductive, and neuropsychiatric endpoints.

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8.6 Evidence

Current GC therapy for CAH is suboptimal because supraphysiological doses are often needed to suppress adrenal androgens. Excess GC places patients at risk for iatrogenic Cushing's syndrome, and lower-dose GC leads to inadequately treated androgen excess. Thus, comorbidities associated with both hypercortisolism and hyperandrogenism should be a part of future studies.

9.0 CAH in Adulthood

Diagnosis of NCCAH in adults

Recommendation

9.1. We recommend that NCCAH screening with an early morning serum 17-OHP be confirmed when needed through an ACTH stimulation test (**1**|⊕⊕○○).

9.1 Evidence

Baseline follicular-phase early-morning 17-OHP levels can be used to detect CAH, but the normal cutoff varies between 200 and 400 ng/dl, depending on the assay (6 and 13 nmol/liter) (167, 218–220). ACTH stimulation is needed for patients with baseline 17-OHP around the cutoff; NCCAH patients reach higher than 1000 ng/dl (33 nmol/liter). Reference values for the local laboratory should be sought. For occasional patients with nondiagnostic values, genotyping (219, 221, 222) may confirm the diagnosis.

Treatment of NCCAH

Recommendation

9.2 We suggest treatment of adults with NCCAH with patient-important hyperandrogenism or infertility (**2**|⊕○○○). We suggest clinicians not prescribe daily GC substitution in adult males with NCCAH (**2**|⊕○○○).

9.2 Evidence

There are no published randomized and controlled trials of various treatments for NCCAH. However, administration of dexamethasone, 0.25 mg/d, can be effective in reducing acne and irregular menstruations within 3 months and hirsutism within 30 months (223). Although fertility in classic CAH is reduced (147, 161), a retrospective multicenter review found that 68% of 203 pregnancies among 101 NCCAH women had occurred before the diagnosis was made, suggesting that GC treatment is not required for fertility. Spontaneous abortions occurred more frequently before treatment in two such studies of referred reproductive endocrinology clinic patients (224, 225). Interestingly, this was not observed in a controlled retrospective Swedish study that included 90% classic CAH women (160). It is difficult to draw definitive conclusions about the need for GC therapy in all NCCAH women based on these limited data; however, treatment may benefit infertile NCCAH women or those with a history of miscarriage.

Testicular adrenal rest tumors are common in adults with classic CAH but seem to be rare in NCCAH. Thus, prophylactic GCs do not seem warranted in men with NCCAH. There is no evidence of clinically significant cortisol deficiency or adrenal crisis in NCCAH, and we do not suggest that previously untreated adults with NCCAH be given substitution during severe stress, unless they have demonstrated a subnormal cortisol response during cosyntropin stimulation.

GC treatment of adults with CAH or NCCAH

Recommendation

9.3 We suggest that adult patients with classic CAH be treated with HC or long-acting GCs (**2**|⊕○○○).

9.3 Evidence

Adults with classic CAH are treated to avoid symptoms of adrenocortical deficiency in both sexes; hyperandrogenism, voice changes, and infertility in women; and testicular tumors in men. However, overtreatment with GCs will cause Cushingoid features, and excess MCs will cause hypertension.

There are no randomized controlled studies on long-term follow-up of different modes of treatment of adults with classic CAH, and practice varies. Among European pediatric endocrinologists, 36% said they used HC (mean dose 13.75 mg/m^2), 14% used prednisolone (4.75 mg/d), and 33% used dexamethasone (0.5 mg/d) as the primary form of GC for substitution in adults with CAH (226). The longer-acting GCs were more commonly used in adults than in children.

Overtreatment with GCs may lead to osteoporosis, as noted in retrospective studies of 62 adult women with CAH, accompanied by an increased incidence of fractures as compared with healthy controls (227). The occurrence and the severity of osteopenia/osteoporosis was not related to CAH genotype or phenotype but probably was due to overtreatment with GCs. Gestational diabetes was increased among CAH women *vs.* controls but without other metabolic or cardiovascular abnormalities (228). Control of hyperandrogenic symptoms in young women may require additional treatment such as antiandrogenic oral contraceptives (142).

The optimal dose of fludrocortisone substitution in adults (as in infants and children) has not been critically studied. The need for MCs decreases with age, because serum aldosterone is high and renal MC receptor mRNA is low at birth (229), and the degree of MC and/or salt

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supplementation must be monitored by blood pressure and renin measurements in blood.

Treatment for hirsutism is beyond the scope of this Guideline and has been discussed separately (142) in another Endocrine Society Guideline.

Monitoring treatment of adults with CAH

Recommendation

9.4 We suggest that monitoring of GC and MC treatment include at least annual physical examination and appropriate hormone measurements.

9.4 Evidence

GC substitution in the adult CAH patient aims to suppress virilization and menstrual disturbance in women, alteration of gonadotropin secretion in both sexes, and testicular adrenal rest tumors in men. Available studies report on small series, and different modes for monitoring treatment have not been studied systematically. Long-term observational studies have been somewhat informative (227, 228, 230, 231). GC overtreatment may cause Cushingoid symptoms, whereas undertreatment may cause Addisonian symptoms. Overtreatment with MCs may cause hypertension; undertreatment may lead to low blood pressure, salt loss, fatigue, and increased requirements for GC replacement.

The principles of monitoring GC treatment in adult CAH patients are similar to those employed in monitoring children. Optimal levels for 17-OHP and androstenedione have not been defined; testosterone levels in men normally reflect gonadal rather than adrenal function and therefore are not useful for monitoring therapy. 17-OHP may be elevated at night, even when morning levels are acceptable. Therefore, home monitoring of salivary 17-OHP may be more informative (232). Men with large testicular adrenal rests may have low morning testosterone indicating poor Leydig cell function (233).

Women with CAH are often overweight, with high blood pressure and hyperinsulinemia, and have risk factors for cardiovascular disease. Although Falhammar *et al.* (228) found that CAH patients over 30 yr of age had a higher waist to hip ratio than age-matched controls, fat mass was similar, and few CAH patients had hypertension, cardiovascular disease, or diabetes. The most significant metabolic abnormality was a 20% prevalence of gestational diabetes.

Conflicting reports concern BMD and risk of fractures. Reports studying adolescents and young adults differ concerning normal *vs.* reduced BMD (227). Chakhtoura *et al.* (234) showed a negative correlation between the accumulated lifetime dose of GC and BMD. All of these factors may reflect the high doses of GCs used to suppress adrenal androgens.

Genetic counseling

Recommendation

9.5 We recommend that genetic counseling be given to parents at birth of a CAH child and to adolescents at the transition to adult care (**1**|⊕○○○).

9.5 Evidence

CAH is autosomal recessive. The genotype and phenotype correlate well; siblings with CAH generally, but not always, have similar symptoms and degrees of female virilization. There is a 25% probability that siblings of the index case will have CAH and a 50% probability that they are asymptomatic carriers. Based on a classical CAH incidence of 1:10,000–1:20,000 (1–4), the incidence of carriers in the general population is 1:50–1:71. Using a median value of 1:60, a patient with classic CAH would have a one in 120 probability of having a child with classic CAH. For NCCAH, about two thirds of patients are compound heterozygotes, carrying one allele that causes classic CAH and one that causes NCCAH. The milder mutation will determine the phenotype; hence, the NCCAH parent has a one in 240 risk of having a child with classic CAH. However, in a retrospective analysis of 162 children born to NCCAH women, the risk was 2.5% (225). Bidet *et al.* (219) found a combined incidence of mild and severe mutations in 8% of partners of French NCCAH patients, suggesting a much higher risk for offspring to have CAH of any form.

9.5 Values and preferences

Genetic counseling is valuable for parents planning for future children. Some adults with CAH may request genotyping for themselves and/or their partner before planning for children. CAH genotyping requires certified laboratories that have adequate quality controls and can sequence the *CYP21A2* gene if screening for the most common mutations is not informative.

Transition to adult care

Recommendations

9.6 We suggest that pediatric, reproductive, and adult endocrinologists, gynecologists, and urologists have joint clinics for transferring CAH patients to adult care (**2**|⊕○○○).

9.7 We suggest a gynecological history and examination under anesthesia in adolescent females with CAH.

9.8 We suggest against the routine use of pelvic US in CAH patients with regular menstrual cycles (**2**|⊕○○○).

9.9 We suggest that males with classic CAH be periodically screened from adolescence for testicular adrenal rest tumors by US (**2**|⊕○○○).

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9.6–9.9 Evidence

Several reviews, but no controlled studies, describe how to transfer CAH patients from pediatric to adult care. Our suggestions are based on clinical experience (235–238).

Adult women with CAH often remember childhood visits to their physician as highly intrusive. After follow-up of the initial surgery, gynecological examinations should be minimized until planning for possible additional surgery.

Adolescent girls with virilizing CAH need gynecological consultation before or during puberty. The adolescent gynecological examination should be done under general anesthesia by an experienced gynecologist, ideally together with the pediatric surgeon/urologist. The patient and her family, in consultation with the surgical team, should decide whether additional surgery is needed. Issues of sexual activity and contraception should be discussed by the pediatric endocrinologist, and fertility should be addressed at the appropriate time by a reproductive endocrinologist. Obstetricians should be aware that despite an apparent normal pregnancy rate of about 90%, classic CAH women have low fecundity (0.25 live births per woman *vs.* 1.8 in the general population) (239).

Pediatric endocrine care is usually transferred to an adult endocrinologist at the end of adolescence, usually coinciding with the completion of secondary school, *i.e.* typically at age 18. A gradual transition of adolescent to adult care would ideally allow the patient's relationship with the adult physician to be consolidated before the patient terminates his or her relationship with the pediatric endocrinologist. Males may require consultation with a urologist if testicular adrenal rest tumors are not amenable to medical therapy and/or physical examination and sonogram document incomplete resolution of an adrenal rest leaving a testicular mass suspicious for cancer.

Counseling about fertility

Recommendation

9.10 We suggest that CAH patients with impaired fertility consult a reproductive endocrinologist and/or fertility specialist (**2**|⊕⊕○○).

9.10 Evidence

Fertility in CAH males is poorly studied (188, 240–242). One study reported normal fertility (188), but others reported substantially reduced fertility (243).

Testicular adrenal rest tumors increase with age in CAH, impairing fertility. The prevalence of these tumors varies between 0 and 94%, depending on the study population (188, 240, 243). (See also *6.1–6.3 Evidence* regarding testicular adrenal rest tumors in boys aged 2–18 with classic CAH.) Undetected adrenal rest tumors may obstruct the seminiferous tubules, causing secondary gonadal dysfunction and infertility. When tumors are unresponsive to steroid therapy, surgical intervention by a testis-sparing procedure with cryopreservation of the semen may be needed, because fertility is uncertain (154, 244). Fertility may be impaired by suppression of gonadotropin secretion by adrenal steroids if adequate doses of GCs are not given (242). Psychosocial factors may also play a role, because fewer men with CAH had steady heterosexual relationships than did age-matched controls (241).

Pregnancy and delivery rates were significantly lower in 62 women with CAH (ages 18–63), despite fertility treatments (160). Only 30% of the women with CAH had ever tried to become pregnant, as compared with 66% of controls. The number of children born to CAH women correlated with CAH genotype; three of six women with NCCAH had children, and nine of 27 women with simple virilizing CAH had children, but only two of 29 women with salt-wasting CAH had children. Hagenfeldt *et al.* (160) summarized this literature, finding an unexplained 2:1 female to male ratio for offspring of CAH women.

Management of CAH and NCCAH during pregnancy

Recommendations

9.11 We suggest that pregnant women with CAH be followed jointly by endocrinologists and obstetricians.

9.12 We recommend that patients with CAH who become pregnant continue their prepregnancy doses of HC/prednisolone and fludrocortisone therapy (**1**|⊕⊕○○). GC doses should be adjusted if symptoms and signs of GC insufficiency occur. We recommend against the use of GCs that traverse the placenta, such as dexamethasone, for treatment of pregnant patients with CAH (**1**|⊕⊕○○). Stress doses of GCs should be used during labor and delivery.

9.11–9.12 Evidence

Androgen and cortisol levels increase gradually during pregnancy (245) due to increases in SHBG and cortisol-binding globulin. Maternal testosterone levels have been used to monitor CAH patients during pregnancy (245). However, higher binding globulins and placental aromatization typically protect the fetus from the potential virilizing effects of maternal androgens. Maternal 17-OHP is elevated in normal pregnancy and hence cannot be used to monitor GC treatment. High progesterone levels during pregnancy might compete for the MC receptor, theoretically requiring increased fludrocortisone doses, but this has not been studied. Dexamethasone and other steroids that are not inactivated by placental 11β-HSD2 should not be used to treat the pregnant woman who is herself affected with CAH. There are scant empiric data and no widely accepted recommendations for the management of

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GC doses in the pregnant CAH patient. Symptoms of adrenal insufficiency, including postural hypotension, may rarely develop in pregnant women with classic CAH. GC and/or fludrocortisone doses should be increased if such signs and symptoms occur. Consideration may be given to increasing the dose of GC and/or fludrocortisone in advance of the development of clinical evidence of adrenal insufficiency in difficult to manage pregnant salt-wasting CAH patients. During labor and delivery, stress doses of GCs should be given, but there are no controlled studies regarding optimal dosing. CAH women are at increased risk for gestational diabetes (160); thus, glucose tolerance should be monitored throughout pregnancy. Overall, the treatment of the pregnant CAH patient should be individualized.

10.0 Mental health

Recommendation

10.1 We suggest that patients with CAH and psychosocial problems associated with disorders of sexual development be referred to mental health staff with specialized expertise in managing such problems (**2**|⊕⊕○○).

10.1 Evidence

Existing clinical guidelines (107, 246–250) recommend interdisciplinary teams involving mental health staff with expertise in managing psychosocial problems specific to disorders of sexual development (DSD). CAH is one specific subtype under the rubric of DSD (250) but should not be equated with other forms of DSD in which outcomes are less well defined. Patients with CAH may experience psychosocial and psychiatric problems that are not specific to CAH. These can usually be managed by standard mental health clinicians. The 46,XX patients with CAH may also have to cope with problems that are more specific to DSD, such as 1) parent/family medical education, parent/family counseling regarding psychosocial prognosis, and managing parents' distress; 2) gender assignment at birth in cases of marked genital virilization; 3) decisions on gender-confirming (not medically necessitated) genital surgery in infancy and early childhood; and 4) referral for psychological gender evaluation and counseling regarding potential gender reassignment of 46,XX CAH patients after infancy and at any later age, when patient-motivated gender change, both female to male and male to female, can occur, albeit rarely (251). Physician-recommended reassignment to female during infancy of erroneously male-assigned 46,XX patients does not require a psychological gender evaluation.

Additional DSD-specific items for counseling patient and family include preparation for surgery, gender-atypical behavior, social fit, bisexual and homosexual attractions (which are somewhat increased in 46,XX CAH women but still limited to a minority) (252), sexual functioning, and general quality of life (QoL) as well as concerns about inappropriate curiosity or frank stigmatization by other family, peers, or lovers in reaction to gender-atypical somatic features. Ideally, such DSD-related problems are managed by mental health staff with expertise in DSD, complemented by clinical guidelines (107, 246–250, 253, 254), educational websites (*e.g.* www.aboutkidshealth.ca/HowTheBodyWorks/Sex-Development-An-Overview.aspx?articleID=7671&categoryID=XS; www.siecus.org), and long-distance consultation with specialists by e-mail or phone. Healthcare providers without such expertise should refer patients to appropriate staff or at least use the resources listed above.

Evaluation of health-related QoL of patients with CAH

Recommendation

10.2 We suggest the development, evaluation, and implementation in long-term clinical trials and in clinical practice of valid and responsive patient-reported assessments of their QoL in response to treatment regimens (**2**|⊕○○○).

10.2 Evidence

QoL is a broad construct with considerable variability in different settings. Instruments to estimate QoL often cover physical, psychological, and social functioning and ratings of satisfaction. Tools to assess health-related QoL were not designed for issues related to DSD or CAH (255); hence, the results of the few studies of QoL in CAH women are somewhat variable.

A Swedish study of 62 women with CAH noted decreased QoL in the sexuality-related domains (184, 256). A Danish study of 70 women with DSD, including some 46,XX CAH women, found impaired QoL and more affective distress in CAH patients (257). In an Australian study, most of the DSD patients including XX women with CAH had positive psychosocial and psychosexual outcomes, although there were some problems with sexual activity (258). An American study that compared 72 females and 42 males with CAH (aged 3–31 yr) and unaffected relatives found no significant differences in psychological adjustment on age-appropriate validated questionnaires (259). A Finnish study found a better health-related QoL in both male and female patients with CAH than in the general Finnish population, despite numerous medical complications; however, 45% of eligible patients did not participate (241). Among 45 German women with CAH (260), the overall QoL of the CAH women did not differ from controls, but significant impairments were found concerning body image and atti-

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tudes toward sexuality, and CAH women were more often single and fewer of them had children than did controls.

See links to *Resources for Clinical Trials on CAH* in Supplemental Material, Appendix 1.

10.1–10.2 Values and preferences

Because patients vary widely in coping with functional impairments, we consider the assessment of QoL of equal importance to the assessment of functional impairment when evaluating the outcome of comprehensive clinical management. Until standard measures that are sensitive to the specific psychosocial issues of patients with DSD and CAH have been developed, clinicians need to adopt existing measures and rating scales from other areas of chronic care.

Relationship between surgical outcome and psychological development

Apart from urinary tract malformations in a minority of CAH girls, genital ambiguity usually does not require urgent surgical intervention. Severely virilized cases may initially be assigned as males, and once such assignment has been made, it may be difficult to reverse, thereby sacrificing fertility. This is especially true in countries where cultural tradition favors males (261). Among 33 46,XX CAH patients raised as males, four identified themselves as female, and three were gender dysphoric (251). In markedly virilized female-raised children, surgical intervention can facilitate heterosexual intercourse and conception, if desired. Fertility and fecundity, although reduced, remain feasible.

Other psychosocial consequences of genital ambiguity have been documented by case reports but not in systematic studies (262). These consequences include perceived incongruence between genital appearance and assigned gender by parents and society, conflicted gender typing by family members, increased curiosity about the patient's genitals and increased stigmatization by others, impaired genital self-image, and impaired bodily self-image associated with short stature, increased weight, and hirsutism. These factors may lead to social withdrawal, especially from situations involving nudity (team sports or medical examinations), and avoidance of romantic interactions and sexual involvement. Despite the presence of atypical genitalia and anecdotal reports of gender dysphoria and psychosexual dysfunction, core female gender identity is generally preserved among CAH girls (263). Of 250 females with CAH who underwent psychological assessments, 5.2% reported gender problems (251).

To prevent adverse psychosocial consequences, clinical management recommendations have typically included corrective genital surgery (feminizing or masculinizing, depending on the gender assignment of the child in early infancy). This policy of gender-confirming surgery has been questioned by reports of surgical complications, including destruction of the neurovascular bundle during clitoral surgery, especially clitorectomy, clitoral atrophy, vaginal stenosis requiring surgical correction in adolescence, and unsatisfactory cosmetic results after pubertal growth due to misalignment of genital structures. In addition, some patients had problems with sexual function (*e.g.* decreased arousability and decreased orgasmic capacity). Recent reports of long-term follow-up studies show variable outcomes including impaired cosmesis and sexual functioning (264–267), and even nonsurgical procedures such as vaginal dilatation can be problematic (268). A patient support group (269) and some ethicists (270) have demanded postponing all such surgery until the patient can give informed consent; some professional activists called for a moratorium on such surgery until better empirical evidence of risks and benefits was available (271). Despite serious deficiencies with the surgical outcome data (small samples, uncertain representativeness, evaluation of cosmesis by the surgeons, inclusion of multiple surgical techniques, and outcome data oriented toward cosmesis rather than sexual function) (262) and the fact that adult women with CAH typically underwent relatively unsophisticated surgical procedures that are no longer used, the outcome is highly variable in terms of cosmesis, function, and patient satisfaction. Even in adult patients, the demand for informed consent appears unrealistic if the patient is sexually inexperienced.

Controlled observational studies are not available to document whether genital surgery prevents adverse psychosocial consequences. The cosmetic results are variably evaluated by patients, who tend to be more critical than their physicians (184, 185). Nevertheless, recent surveys of women with CAH showed that most favored genital surgery before adolescence (184, 185). We cannot yet know whether improvements in surgical techniques in the last decade will yield improvements in cosmesis and functional outcomes.

Finally, in contemplating the avoidance of early genital surgery, one must also consider that no studies have been conducted to demonstrate that potential adverse psychosocial consequences of gender-incongruent genital appearance can be ameliorated by psychological counseling or psychotherapy. Physicians should inform families of all these concerns and allow them to reach a reasoned decision with input from various sources, including patient and family support groups.

Supplemental Information

A complete description of how the evidence-based recommendations were developed may be found in Supple-

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mental Data, Appendix 2. For a list of all recommendations included in this guideline, see Summary of Recommendations in Supplemental Data, Appendix 3.

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