Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2012 December ; 19(6): 483–488. doi:10.1097/MED.0b013e32835a1a1b.

Management of Congenital Adrenal Hyperplasia in Childhood

Mimi S. Kim, MD,

Children's Hospital Los Angeles, Center for Endocrinology, Diabetes, and Metabolism

Anna Ryabets-Lienhard, DO, and

Children's Hospital Los Angeles, Center for Endocrinology, Diabetes, and Metabolism

Mitchell E. Geffner, MD

Children's Hospital Los Angeles, Center for Endocrinology, Diabetes, and Metabolism

Abstract

Purpose of review—Congenital adrenal hyperplasia (CAH) can present management challenges to the pediatric clinician. Glucocorticoid replacement remains the cornerstone of treatment; however, there are new formulations and delivery mechanisms being studied. Clinicians continue to discuss the optimal treatment of patients from the prenatal stage, through infancy to adulthood. As well, the role of genetics in the clinical care of patients with CAH, and screening for complications, remain topics of discussion. This review will highlight advances made in the past year, as they pertain to the management of pediatric patients with CAH.

Recent findings—This article covers recent studies pertaining to optimal medication regimens, including prenatal dexamethasone treatment; medication delivery; monitoring of hormonal control; and the role of genotyping and genetics in the management of children with CAH.

Summary—Much remains to be learned about the optimal management of children with CAH, including fludrocortisone replacement in simple-virilizing patients, frequency of and specific monitoring strategies (e.g., electrolytes, bone age, *etc.*), catecholamine status, stress-dosing in non-classical adrenal hyperplasia, and early screening for complications or metabolic sequelae. Further randomized, prospective studies are needed to address these issues.

Keywords

Congenital adrenal hyperplasia; CAH; NCAH; childhood; treatment

Introduction

The clinical management of congenital adrenal hyperplasia (CAH) in childhood and adolescence mandates a delicate balance in order to avoid hyperandrogenism and hypercortisolism [1].

Normal growth and puberty are major considerations, with a main outcome of treatment in childhood being attainment of a normal adult height, but there are also other considerations such as treatment with dexamethasone in the prenatal stage, optimal delivery of hydrocortisone, measurement of and reliance on hormone analytes and bone age to assess treatment control, and the role of genotyping and genetics in the management of CAH. The majority of cases of CAH are due to a deficiency in the 21-hydroxylase enzyme (21-OHD), with a clinical spectrum – ranging from most to least severe – consisting of classical [salt-

wasting and simple-virilizing (SV)] to non-classical (NCAH) forms, depending on the mutations of the *CYP21A2* gene present. Patients with 21-OHD will be the focus of this review.

We will discuss updates in management of CAH in childhood, with regard to optimal medication treatment (prenatal dexamethasone treatment, hydrocortisone dosing during infancy, and adjunctive growth hormone), monitoring, medication delivery, and genetics. We recommend that two sets of guidelines published in 2010, one targeting the management of patients with CAH [2] and a second emphasizing delivery of comprehensive care to these patients [3], be read for more detail.

Optimal Glucocorticoid Treatment

The treatment of CAH has not changed significantly over decades, with glucocorticoid replacement and mineralocorticoid replacement (in certain individuals) remaining the mainstays of therapy. We will discuss new developments with regard to growth hormone therapy, hydrocortisone treatment in infancy, and prenatal dexamethasone treatment of expectant mothers.

Prenatal Dexamethasone Treatment

Prenatal dexamethasone treatment is an effective therapy to reduce virilization of the external genitalia in females affected with classical CAH due to 21-OHD. Currently, consensus guidelines recommend that prenatal dexamethasone treatment remains an experimental therapy due to lack of long-term outcome (both efficacy and safety) data.

Hirvikoski et al [4] discussed their experience and outcomes of a prospective, non-randomized, multi-center study from European centers ongoing since 1999, on both mothers and 31 children. In this report, they emphasized the continued need to perform prenatal dexamethasone treatment of fetuses at risk for CAH only within the scope of institutional review board-approved clinical trials and the requirement for long-term follow-up of treated individuals, with comparison of behavioral and somatic outcomes to those of untreated controls. As well, they stressed the need for additional retrospective studies of treated fetuses, rather than solely awaiting long-term prospective outcome study results. They also reported on long-term cognitive outcomes in children treated prenatally with dexamethasone [5]. Fetuses exposed to dexamethasone treatment during the first trimester later exhibited impaired verbal working memory that was associated with a low self-perceived scholastic competence, along with increased social anxiety on self-rating. Boys with short-term prenatal exposure showed less masculine, more gender-neutral behavior on a survey. The group recommended long-term follow-up studies, and larger cohort studies to further and more conclusively assess the safety of this treatment. A commentary by Witchel and Miller [6] echoes these recommendations as well.

A prospective, observational cohort study was reported which included comparisons of neuropsychological testing of 67 dexamethasone-treated children (8 CAH girls), compared to 73 unexposed (15 CAH girls) children [7]. Although the group did not reproduce a previously reported adverse effect on working memory from short-term prenatal exposure to dexamethasone, they raised concerns about long-term exposure to dexamethasone and effects noted on cognitive function in girls with CAH. It was concluded that further study in a larger cohort is necessary.

New techniques that allow karyotyping the fetus by examining fetal cells in the maternal circulation [8] could shorten the time of exposure to dexamethasone [9].

Hydrocortisone Treatment in Infancy

A relatively low-dose hydrocortisone regimen (9–15 mg/m²/day body surface area) was studied in 51 infants with classical CAH during their first three years of life by Bonfig *et al* [10]. The majority of children were salt-wasters and received fludrocortisone as well. The birth length standard deviation score (SDS) was initially higher than that of the reference population, with a slight decrease in linear growth velocity during the first 9 months of life, and a decline in height SDS over time. However, the height SDS at 3 years of age fell within the genetic height potential (target height), and the bone age was appropriate for chronological age for both boys and girls. It was postulated that growth velocity was initially affected by glucocorticoid treatment, perhaps due to extreme sensitivity to this treatment during infancy, and the relatively low hydrocortisone dose used could still be too high during infancy. The same group also reported an insensitivity to androgens in male infants with SV CAH [11] during their first 6 months of life, in a retrospective analysis of the pre-treatment growth of 13 boys diagnosed late, prior to more robust newborn screening practices. The growth velocity was not markedly increased in these boys with SV-CAH during their first 6 months of life, as indicated by growth records obtained from their pediatricians. However, after the first 6 months of life, linear growth velocity increased significantly [birth length was $+0.1 \pm 0.8$ SDS (mean $\pm$ SD)] and, at 4 years of age, height was $+1.8 \pm 1.2$ SDS, with a concomitant advancement in bone age (accelerated to 9.4 ± 4 years at diagnosis). An absence of increased growth velocity in the first year of life in untreated patients with SV CAH had been previously reported [12].

Growth Hormone Treatment

The addition of growth hormone (GH) as an adjunct to the treatment regimen of children with CAH (to maximize adult height) was further explored by Lin-Su, *et al* in a non-randomized prospective study, comparing GH alone with GH in combination with a gonadotropin-releasing hormone agonist (GnRHa) to delay central puberty [13]. The final adult height of 34 children with 21-OHD treated with GH was improved by either GH alone or GH + GnRHa together. There was a greater height discrepancy (predicted vs. adult height) seen at baseline prior to treatment in males, which could explain the shorter mean final height of males (4 cm below their mid-parental target height), compared to females who exhibited a mean final adult height of only 0.6 cm less than their mid-parental target height. Height gain on GH or GH + GnRHa treatment did not appear to be affected by gender or type of CAH (classical vs. NCAH), but was affected by adrenal control. The same group also published a review of the topic [14]. Another retrospective study also examined the near-final height in 13 patients with either classical or NC forms of CAH, following treatment with GH + GnRHa [15]. It was noted that with treatment, the height SDS for bone age improved significantly, which after two years of treatment became similar to the target height.

Medication Delivery and Formulations

The delivery of hydrocortisone orally for daily replacement therapy has remained the mainstay of treatment of CAH for over 30 years. There continues to be interest in achieving a physiological circadian rhythm with daily hydrocortisone replacement therapy. There had been a preliminary study of a modified-release preparation, Chronocort™ (Diurnal, Cardiff, UK), in patients with CAH [16], with advances in characterizing this formulation summarized this past year [17]. Although the pharmacokinetics desired for patients with CAH would differ, another dual-release formulation of hydrocortisone, Plenadren™ (DuoCort/ViroPharma, Helsingborg, Sweden), was tested in a European prospective, cross-over study of patients with adrenal insufficiency as once-daily dosing, compared to thrice-daily dosing [18], with encouraging results with regard to metabolic control. Further studies

in children with either preparation [19], and consideration of other methods of delivery such as subcutaneous infusion [20], are required.

Clinical Monitoring and Diagnosis

The clinical management of patients with CAH depends on an accurate diagnosis of the condition and reliable laboratory assays for subsequent monitoring. We will discuss advances in newborn screening, 17-hydroxyprogesterone (17OHP) assays, and the diagnosis of NCAH.

Newborn Screening

The clinical management of CAH has changed with the mandate of newborn screening in all 50 states in 2008, with earlier diagnosis of babies with CAH. There have been continued efforts to address the high false-positive rates associated with fluoro-immunoassay testing of 17OHP, due to cross-reacting steroids, with second-tier testing and adjusted cut-offs for 17OHP. The French assessment of the efficiency of their newborn screening program between 1996–2003 led to the conclusion that they could stop screening premature babies [21]. As an adjunctive or alternative method, the emergence of newborn screening using tandem mass spectrometry, was addressed by Janzen et al [22]. Quantification of several steroids (17OHP, 21-deoxycortisol, 11-deoxycortisol, 11-deoxycorticosterone, and cortisol) extracted from dried blood spots by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) gave linear results for all steroids over a range of 5–200 nmol/L (cortisol: 12.5–500 nmol/L), coefficients of regression >0.992, and an inter-assay coefficient of variation (CV) of <3%. Unlike the immunoassay method, UPLC-MS/MS was not affected by cross-reacting steroids. Also to consider are false-negative results with the current methodology [23], although the etiology remains unclear.

17OHP Assays

There continues to be discussion amongst clinicians regarding the specific analytes that should be followed in order to determine optimal hormonal control in patients with CAH, along with the best time of day for these tests to be measured, and daily hormone profiles. The diagnostic validity of salivary 17OHP measures for the monitoring of adrenal control was studied, as compared to serum samples collected simultaneously in 23 adolescents and young adults with CAH [24]. Salivary sampling would offer the benefit of painless sampling, and provide a measure of bioactive free hormone. In comparing daily profiles, it appeared that saliva analysis was a more sensitive measure than serum, in the assessment of adequacy of treatment. Interestingly, a single 17OHP value measured at 0700 hours did not allow for a reliable assessment, with the need for modification of treatment only becoming evident with whole-day hormonal profiling. Salivary sampling has been [25] and continues to be studied as a potential alternative to serum testing [26], with variable results.

As well, dried blood spots were used to study steroid profiling with liquid chromatography-tandem mass spectrometry in patients with CAH, as an alternate source to serum [27]. There was an excellent correlation between the dried blood spots and serum testing, leaving open the possibility of utilizing this methodology in clinical care in the future.

Diagnosis of Non-classical CAH

Confirmatory 17OHP testing, most likely with a high-dose ACTH (Cortosyn™) stimulation test, is necessary for the diagnosis of the NC form of 21-OHD. Other clinical and molecular parameters may be used as well. Interestingly, a study of 24 patients with NCAH did not find a significant growth velocity acceleration in untreated patients [28]. However, the bone age acceleration was more pronounced, and could be useful in a clinical diagnostic

assessment of these patients. An update on treatment of NCAH patients is covered by Trapp *et al* [29].

Genetics

Genotyping as an adjunctive molecular test in the diagnosis of the patient with CAH is possible commercially. The 2010 Consensus Guidelines [2] recommended that, should genotyping be performed, testing be done by certified laboratories with adequate quality controls and the ability to sequence the *CYP21A2* gene, if necessary. Genetic counseling can help parents of a child with CAH, and adults with CAH, plan for future children. Insurance coverage may make it difficult to routinely genotype patients with CAH, as the cost ranges from \$500–1000 at three major diagnostic laboratories in the U.S., and access to sequencing could be variable. However, emerging genotyping studies may make it more important to incorporate genotyping into clinical care for the future, perhaps even as early as the newborn screening stage [30]. A comprehensive *CYP21A2* analysis, utilizing targeted mutation analysis and sequencing as necessary in a large cohort of 213 patients with CAH and 232 parents from 182 unrelated families [31], revealed accurate genotype-based prediction of phenotype in 90.5% of patients with salt-wasting mutations and in 85.1% of those with simple-virilizing mutations; 10% of patients did not have an identifiable mutation on one allele. There are complex gene variations in this monogenic disorder, including compound heterozygosity in 79% of CAH patients and in 69% of NCAH patients (involving one NCAH and one classical mutation), duplicated haplotypes, *de novo* mutations, and even uniparental disomy. A second genotyping study of a large cohort of 454 Argentinean patients, using an 11-mutation screen with sequencing as necessary, also showed a high genotype-phenotype correlation [32].

Further specific analysis may help elucidate genotype-phenotype discrepancies, such as junction site analysis of the chimeric *CYP21A1P/CYP21A2* genes that are commonly seen in patients with CAH due to 21-OHD [33]. Genotype-phenotype discrepancies of three patients in a cohort of 202 patients were explained by this comprehensive junction site analysis. As well, functional studies could be added to the clinical and molecular picture, with enzyme activity studied *in vitro* [34].

Screening for Comorbidities

Screening for longer-term comorbidities expected in adulthood in pediatric CAH patients is a strong clinical consideration. The presence of testicular adrenal rest tissue (TART) should be considered in adolescents with classical CAH, and perhaps also in younger boys. Bone health should be maximized, but there is not yet much effect of glucocorticoid treatment noted in children with CAH [35]. Screening for metabolic disease risk factors in childhood remains in question. A comprehensive review of studies to-date examining comorbidities in CAH was published recently by Reisch *et al* [36]. Vascular endothelial and smooth muscle dysfunction, using flow-mediated dilatation and glyceryl tri-nitrate dilatation, was found to be present in adolescence [37]. Although this group did not note an increased intima-media thickness (IMT) compared to controls, a larger IMT was noted in Italian adolescents compared to controls [38].

Conclusion

There remains a need to optimize standard treatment of pediatric patients with CAH in order to decrease potential morbidity associated with glucocorticoid treatment. More prospective studies examining adjunctive therapies such as growth hormone, and different doses of hydrocortisone across childhood and adolescence, are necessary to draw definitive conclusions. As well, further large prospective and retrospective studies of the long-term

effects of prenatal dexamethasone treatment are required. Finally, there are potentially exciting advances in assay methodology for newborn screening and monitoring of clinical care.

Acknowledgments

CARES Foundation and The UCLA Foundation David L. Abell and Barbara Abell Donor-Advised Fund.

Grants and support not exclusive to this submission: MSK is a KL2 Scholar through the SC CTSI, Keck School of Medicine of USC, NIH Grant Award Number KL2RR031991. MEG: NIDDK, NICHD, National Institute of Nursing Research, California Department of Health Services, Daiichi-Sankyo (clinical trial consultant), Eli Lilly, Inc. (research grant and research contract), Endo Pharmaceuticals (advisory board), Genentech, Inc. (research grant), Ipsen (data safety monitoring board and research contract), Merck-Serono (advisory board), Novo Nordisk (research grant and research contract), and Pfizer, Inc. (research contract and advisory board).

References

1. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. *lancet*. 2005; 365:2125–2136. [PubMed: 15964450]
2. Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010; 95:4133–4160. [PubMed: 20823466]
3. Auchus RJ, Witchel SF, Leight KR, et al. Guidelines for the Development of Comprehensive Care Centers for Congenital Adrenal Hyperplasia: Guidance from the CARES Foundation Initiative. *Int J Pediatr Endocrinol*. 2010; 2010:275213. [PubMed: 21274448]
- *4. Hirvikoski T, Nordenstrom A, Wedell A, et al. Prenatal Dexamethasone Treatment of Children at Risk for Congenital Adrenal Hyperplasia: The Swedish Experience and Standpoint. *J Clin Endocrinol Metab*. 2012; 97(6):1881–1883. This paper described experience with prenatal dexamethasone treatment in Sweden, which raised concerns for potential risks and side effects associated with prenatal dexamethasone treatment in children at risk for CAH. [PubMed: 22466333]
- *5. Lajic S, Nordenstrom A, Hirvikoski T. Long-term outcome of prenatal dexamethasone treatment of 21-hydroxylase deficiency. *Endocr Dev*. 2011; 20:96–105. This study raised concerns for potential adverse long-term effects of dexamethasone-exposed children at risk for CAH. This study urges for larger studies to be conducted to evaluate long-term effects of prenatal dexamethasone treatment. [PubMed: 21164263]
- *6. Witchel SF, Miller WL. Prenatal Treatment of Congenital Adrenal Hyperplasia-Not Standard of Care. *J Genet Couns*. 2012 May 26. [Epub ahead of print] This study evaluated the safety and ethical considerations of prenatal dexamethasone treatment. It concluded that this experimental therapy should only be done in prospective trials approved by ethical review boards.
- *7. Meyer-Bahlburg HF, Dolezal C, Haggerty R, et al. Cognitive outcome of offspring from dexamethasone-treated pregnancies at risk for congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Eur J Endocrinol*. 2012; 167:103–110. This study found potentially adverse effects on cognitive function in CAH females with long-term prenatal dexamethasone exposure. [PubMed: 22549088]
- *8. Simpson JL, Bischoff F. Novel non-invasive prenatal diagnosis as related to congenital adrenal hyperplasia. *Adv Exp Med Biol*. 2011; 707:37–38. This paper described risk-free non-invasive techniques for prenatal diagnosis of genetic disorders using either intact fetal cells or cell-free fetal DNA in maternal blood. [PubMed: 21691950]
- *9. Hindmarsh PC. Endocrine Society Congenital Adrenal Hyperplasia Guidelines: great content but how to deliver? *Clin Endocrinol (Oxf)*. 2012; 76:465–466. This is a commentary discussing guidelines for treating CAH and their impact on patients and health care. [PubMed: 22077918]
- *10. Bonfig W, Schmidt H, Schwarz HP. Growth patterns in the first three years of life in children with classical congenital adrenal hyperplasia diagnosed by newborn screening and treated with low doses of hydrocortisone. *Horm Res Paediatr*. 2011; 75:32–37. This study found that with low doses of hydrocortisone treatment (9–15 mg/m² body surface area) during the first 9 months of

life, growth velocity decreases, and H-SDS was able to approach the genetic height potential. [PubMed: 20714115]

- *11. Bonfig W, Schwarz HP. Growth pattern of untreated boys with simple virilizing congenital adrenal hyperplasia indicates relative androgen insensitivity during the first six months of life. *Horm Res Paediatr.* 2011; 75:264–268. This study found that boys in the first 6 months of life are relatively insensitive to androgens with no increase in height velocity. However, there was a marked increase in height velocity afterwards, which raised possible implications for reduced hydrocortisone doses in the first 6 months of life. [PubMed: 21196707]
12. Claahsen-van der Grinten HL, Noordam K, Borm GF, Otten BJ. Absence of increased height velocity in the first year of life in untreated children with simple virilizing congenital adrenal hyperplasia. *J Clin Endocrinol Metab.* 2006; 91:1205–1209. [PubMed: 16464952]
- *13. Lin-Su K, Harbison MD, Lekarev O, et al. Final adult height in children with congenital adrenal hyperplasia treated with growth hormone. *J Clin Endocrinol Metab.* 2011; 96:1710–1717. This study's results showed a benefit of GH treatment with or without LHRHa in improving final adult height in patients with CAH. [PubMed: 21450983]
14. Harbison MD, Lin-Su K, New MI. Growth hormone treatment in children with congenital adrenal hyperplasia. *Adv Exp Med Biol.* 2011; 707:107. [PubMed: 21691965]
15. Longui CA, Kochi C, Calliari LE, et al. Near-final height in patients with congenital adrenal hyperplasia treated with combined therapy using GH and GnRHa. *Arq Bras Endocrinol Metabol.* 2011; 55:661–664. [PubMed: 22218451]
16. Verma S, Vanryzin C, Sinaii N, et al. A pharmacokinetic and pharmacodynamic study of delayed- and extended-release hydrocortisone (Chronocort) vs. conventional hydrocortisone (Cortef) in the treatment of congenital adrenal hyperplasia. *Clin Endocrinol (Oxf).* 2010; 72:441–447. [PubMed: 19486026]
- *17. Debono M, Ross RJ. Optimal glucocorticoid therapy. *Endocr Dev.* 2011; 20:173–180. This study evaluated therapeutic effects of Chronocort in simulating the overnight rise in cortisol release and in controlling morning androgen levels in patients with CAH. [PubMed: 21164270]
18. Johannsson G, Nilsson AG, Bergthorsdottir R, et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. *J Clin Endocrinol Metab.* 2012; 97:473–481. [PubMed: 22112807]
- *19. Osorio J. Adrenal gland: New dual-release hydrocortisone tablet for adrenal insufficiency. *Nat Rev Endocrinol.* 2012; 8:67. The new dual-release hydrocortisone tablet received market authorization in the European Union in November 2011, is currently being assessed in a phase IIIb study.
20. Tuli G, Rabbone I, Einaudi S, et al. Continuous subcutaneous hydrocortisone infusion (CSHI) in a young adolescent with congenital adrenal hyperplasia (CAH). *J Pediatr Endocrinol Metab.* 2011; 24:561–563. [PubMed: 21932600]
21. Coulm B, Coste J, Tardy V, et al. Efficiency of neonatal screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency in children born in mainland France between 1996 and 2003. *Arch Pediatr Adolesc Med.* 2012; 166:113–120. [PubMed: 22312171]
- *22. Janzen N, Sander S, Terhardt M, et al. Rapid steroid hormone quantification for congenital adrenal hyperplasia (CAH) in dried blood spots using UPLC liquid chromatography-tandem mass spectrometry. *Steroids.* 2011; 76:1437–1442. This study evaluated efficacy of dried blood spots for the rapid and sensitive screening of CAH. [PubMed: 21839763]
23. Sarafoglou K, Banks K, Kylo J, et al. Cases of congenital adrenal hyperplasia missed by newborn screening in Minnesota. *JAMA.* 2012; 307:2371–2374. [PubMed: 22692165]
- *24. Deutschbein T, Unger N, Hauffa BP, et al. Monitoring medical treatment in adolescents and young adults with congenital adrenal hyperplasia: utility of salivary 17alpha-hydroxyprogesterone day profiles. *Exp Clin Endocrinol Diabetes.* 2011; 119:131–138. This study evaluated efficacy of salivary 17OHP for monitoring medical treatment in patients with CAH, with samples collected at 7 time points throughout a day. [PubMed: 20690075]
25. Dauber A, Kellogg M, Majzoub JA. Monitoring of therapy in congenital adrenal hyperplasia. *Clin Chem.* 2010; 56:1245–1251. [PubMed: 20558634]

26. Juniarto AZ, Goossens K, Setyawati BA, et al. Correlation between androstenedione and 17-hydroxyprogesterone levels in the saliva and plasma of patients with congenital adrenal hyperplasia. *Singapore Med J.* 2011; 52:810–813. [PubMed: 22173250]
27. Sarafoglou K, Himes JH, Lacey JM, et al. Comparison of multiple steroid concentrations in serum and dried blood spots throughout the day of patients with congenital adrenal hyperplasia. *Horm Res Paediatr.* 2011; 75:19–25. [PubMed: 20798478]
28. Pijnenburg-Kleizen KJ, Borm GF, Otten BJ, et al. Absence of clinically relevant growth acceleration in untreated children with non-classical congenital adrenal hyperplasia. *Horm Res Paediatr.* 2012; 77:164–169. [PubMed: 22508177]
- *29. Trapp CM, Oberfield SE. Recommendations for treatment of nonclassic congenital adrenal hyperplasia (NCCAH): an update. *Steroids.* 2012; 77:342–346. This paper reviewed and discussed the genetics and phenotypic variability in patients with NCCAH comparing treated and untreated patients. [PubMed: 22186144]
30. Sarafoglou K, Lorentz CP, Otten N, et al. Molecular testing in congenital adrenal hyperplasia due to 21alpha-hydroxylase deficiency in the era of newborn screening. *Clin Genet.* 2012; 82:64–70. [PubMed: 21534945]
- *31. Finkelstein GP, Chen W, Mehta SP, et al. Comprehensive genetic analysis of 182 unrelated families with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab.* 2011; 96:E161–172. This paper has performed an extensive genetic analysis in 213 patients and 232 parents from 182 unrelated families, concluding that due to the high frequency of complex genetic variation in CAH a more detailed genetic analysis is required to determine a genotype in those patients. [PubMed: 20926536]
32. Marino R, Ramirez P, Galeano J, et al. Steroid 21-hydroxylase gene mutational spectrum in 454 Argentinean patients: genotype-phenotype correlation in a large cohort of patients with congenital adrenal hyperplasia. *Clin Endocrinol (Oxf).* 2011; 75:427–435. [PubMed: 21609351]
33. Chen W, Xu Z, Sullivan A, et al. Junction site analysis of chimeric CYP21A1P/CYP21A2 genes in 21-hydroxylase deficiency. *Clin Chem.* 2012; 58:421–430. [PubMed: 22156666]
34. Barbaro M, Soardi FC, de Mello MP, et al. Functional studies of CYP21A2 mutants complement structural and clinical predictions of disease severity in CAH. *Clin Endocrinol (Oxf).* 2012; 76:766–768. [PubMed: 22040027]
35. Cetinkaya S, Kara C. The effect of glucocorticoid replacement therapy on bone mineral density in children with congenital adrenal hyperplasia. *J Pediatr Endocrinol Metab.* 2011; 24:265–269. [PubMed: 21823521]
36. Reisch N, Arlt W, Krone N. Health problems in congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Horm Res Paediatr.* 2011; 76:73–85. [PubMed: 21597280]
37. Harrington J, Pena AS, Gent R, et al. Adolescents with congenital adrenal hyperplasia because of 21-hydroxylase deficiency have vascular dysfunction. *Clin Endocrinol (Oxf).* 2012; 76:837–842. This study showed that adolescents with CAH have vascular dysfunction by finding significantly reduced FMD, and elevated systolic blood pressure; but no difference in cIMT. [PubMed: 22145701]
38. Wasniewska M, Balsamo A, Valenzise M, et al. Increased Large Artery Intima Media Thickness in Adolescents with Either Classical or Non-Classical Congenital Adrenal Hyperplasia. *J Endocrinol Invest.* 2011

Key points

- Prenatal dexamethasone treatment (administered to mothers) of female fetuses with CAH due to 21-OHD is an effective therapy to reduce virilization of the external genitalia; such treatment, however, remains experimental due to lack of long-term outcome data.
- Optimal dosing of hydrocortisone in infants with CAH requires further study, as do dual-release and slow-release formulations.
- Adjunctive therapies (such as growth hormone with or without the addition of a gonadotropin-releasing hormone agonist) to maximize adult height appear promising, but cannot be considered standard-of-care.
- Newer newborn screening strategies and improved laboratory assays (using mass spectrometry) and genetic tools allow for improved diagnostic sensitivity and stratification into classical and non-classical forms of CAH secondary to 21-OHD.