

## Height Outcome in Congenital Adrenal Hyperplasia Caused by 21-OH Deficiency: A Meta-Analysis

There are reports in the literature of significant short final height associated with virilizing congenital adrenal hyperplasia (CAH). These final heights, which average  $-2$  standard deviations (SD) or lower, are not related to the dose of glucocorticoid, degree of hormonal control achieved, or age at initiation of therapy. Eugster and colleagues review their experience regarding adult height in 65 of their CAH patients over a 20-year period. To be included in their study, children had to be 5 years of age or older. Age at diagnosis, target height, and adult final height were examined. Early diagnosis was defined as a diagnosis made at less than 1 year of age. Actual and predicted height values were expressed as SD scores, and compliance was assessed by querying physicians. For patients who had not yet reached adult height, predictions of adult height were derived using the child's most recent bone age. Of the 65 patients whose charts were examined, 23 had completed their linear growth, and compliance was judged to be good in 28. The overall mean final height SD score minus the target height SD score was  $-1.03$  ( $-4.21$  to  $-2.32$ ). There was no difference seen between males and females. However, a trend (not statistically significant) for better height outcome was seen in patients with good compliance. Those patients identified as having been diagnosed early tended to have a better final height minus target height SD score than those identified later (again, not statistically significant).

In addition, a Medline database search was conducted of all publications reporting height outcome in CAH patients. The meta-analysis identified 16 studies with data that could be used to provide similar outcome information. The current study was added to those data (see Figure). The mean weighted final height SD score for all studies was  $-1.7$ ; in the subset of studies in which target height could be determined, the final height minus target height SD score was  $-1.21$ . In this larger group, a statistically significant difference was seen between patients who were diagnosed early versus late.

The authors state that their data, as well as that from the meta-analysis, demonstrate that adult stature within 1 SD of genetic target may be achieved by many CAH patients with the use of traditional therapy. Also, those subjects diagnosed at an early age have a significantly better outcome than those identified later, and compliance appears to confer some advantage in final height. They correctly point out the flaws in their analyses, including the retrospective design, the prediction of final height in two thirds of the subjects as opposed to actual measurements, and the subjective evaluation of compliance. They stress, however, that rather than pursuing alternative therapies for CAH, efforts should be focused on early detection and improved compliance.

Eugster EA, et al. *J Pediatrics* 2001;138:26-32.

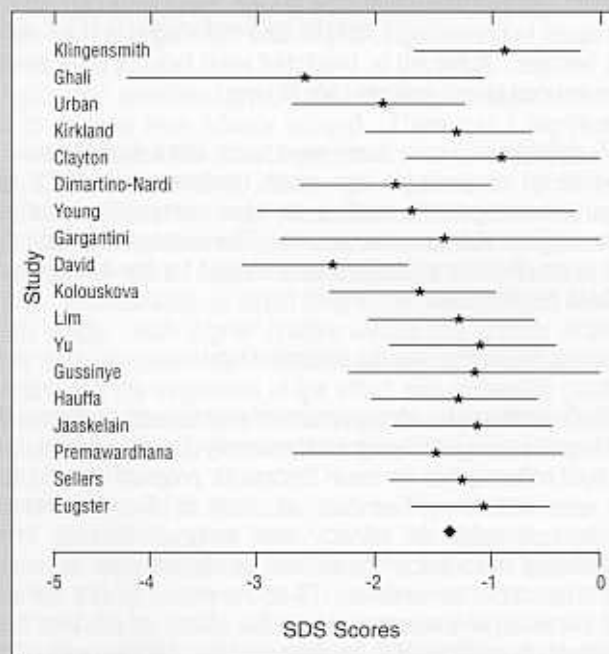
**Editor's comment:** The information provided by this study should be of considerable interest to all pediatric endocrinologists. The flaws in the data, as emphasized by the authors, are significant, even though the results of their particular study are similar to those in the literature. Presenting information regarding final height when that height is a predicted value for more than two thirds of the subjects makes the results highly speculative.

*Indeed, those subjects who are still growing—6 of whom were teenagers—may have had changes in their compliance that later could have affected their adult height. Closing the door on alternative therapy suggests that some physicians may be better at securing compliance in their patients. A previous article in GGH (2001;15(3):33-41) reviews the adult consequences of CAH. This review, which included 5 of the studies listed in the current article, showed that nearly all subjects were shorter than expected, with little influence of age at diagnosis on outcome. Although these data should not be construed as refuting the conclusions provided by Eugster et al, nonetheless there is considerable variability in outcome in different clinics and, presumably, among different patient groups. Indeed, decreased adult height has been correlated with increased body weight and body mass index (BMI) during childhood, suggesting that those children who may be overtreated in attempts to suppress androgen production may have a significant risk of reduction in final height. Clearly, those patients could have benefited from alternative treatments.*

William L. Clarke, MD

**2nd Editor's comment:** Achievement of optimal growth in children with CAH is a well-recognized challenge in the treatment of this disorder. Often there is an inability to adequately suppress

Figure  
Overall Mean SD Score of Final Height for Each Study in Meta-Analysis With 95% CI



Solid diamond indicates weighted mean SD score for all studies. Also demonstrated is lack of correlation between year of publication and outcome.

Reprinted with permission from Eugster EA, et al. *J Pediatrics* 2001; 138:26-32.

corticotropin stimulation without simultaneously incurring the deleterious effect on growth of glucocorticoid overtreatment. This study clearly points out that adult stature in most children with CAH is within 1 SD of the genetic target, with at least one third of the patients achieving their target height. This study reassures pediatric endocrinologists that adequate treatment of patients diagnosed early might lead to achievement of an adult height appropriate for the family. However, there might be opportunities for advances in clinical management combined with diagnostic precision by the molecular genetic characterization of these patients, ie, the CYP21 gene. The heterogeneity of the disease and/or the concept that all patients with CAH need treatment with mineralocorticoid replacement, regardless of their salt-wasting status, needs to be considered to improve the outcome. However, the most practical item is for us to devise ways to

improve compliance with the treatment over prolonged periods. For example, it was recently shown that treatment with dexamethasone in a convenient once-a-day dosage may be easier for the patients and yet allow them to achieve a normal growth (see the next abstract for details).

Fima Lifshitz, MD

**3rd Editor's comment:** The reader's attention is redirected to Dr. Clarke's comments above pertaining to BMI, increased body weight, and adult height. After rereading, proceed to an abstract in this issue entitled, "Body Mass Index in Childhood and Its Association With Height Gain, Timing of Puberty, and Final Height."

Robert M. Blizzard, MD

## Dexamethasone Treatment of Virilizing Congenital Adrenal Hyperplasia (VCAH): The Ability to Achieve Normal Growth

The authors summarize their 2 decades of experience with the long-term, routine use of dexamethasone (DEX) in the treatment of children with 21-hydroxylase- and 11-hydroxylase-deficient CAH (N=26 [23 with salt loss] and 5, respectively). Administration of DEX began as early as birth and continued for an average of 7 to 8 years and for as long as 20 years. DEX elixir was administered once daily (0.1 mg/mL) at a mean dose of 0.27 mg/m<sup>2</sup>/d (range, 0.24 to 0.33 mg/m<sup>2</sup>/d). Fludrocortisone was given as needed. The hypothalamic-pituitary-adrenal axis was effectively suppressed with this regimen.

In the 19 subjects whose bone age was within 2 years of chronologic age at the initiation of DEX, there were comparable increases in chronologic, height, and bone ages in both males and females. Achieved or predicted adult heights were similar to estimated target heights (see Figure).

In 7 children in whom bone ages were more than 2 years in advance of chronologic age when treatment with DEX was begun, linear growth relative to advancement in bone age improved but did not achieve unity. The authors conclude that DEX is an effective and safe glucocorticoid for the management of CAH in childhood.

Rivkees SA, Crawford JD. *Pediatrics* 2000;106:767-773.

**Editor's comment:** Management of infants and children with CAH remains a challenging task primarily because of the need for rigid adherence to the usual therapeutic program—particularly the administration of cortisol at close to 8-hour intervals. While achievable in infancy and early childhood, strict compliance becomes more difficult as the patients' schooling and other activities increase. Thus, the report by Drs. Rivkees and Crawford is welcome and useful. Many of us have been reluctant to utilize DEX in infants and children with CAH, although it is effective in older adolescents and young adults, because of its evident biopotency. Based on their experience, the authors calculated that 1 mg of DEX is 70-fold more effective than 1 mg of cortisol in suppressing adrenal function, rather than the 30-fold potency stated by the manufacturers.

As the authors point out, a comparison of the effects of DEX to those of another group of children with CAH treated more conventionally would have been useful. It would seem reasonable to undertake such a comparative long-term trial, if possible. Assuming these data are confirmed, DEX would seem preferable to the use of androgen receptor blockers and aromatase inhibitors in the management of children with CAH in order to keep treatment as uncomplicated as possible.

Allen W. Root, MD

