The Journal of Clinical Endocrinology & Metabolism, 2025, **110**, e2171–e2182
https://doi.org/10.1210/clinem/dgae824
Advance access publication 3 December 2024
Clinical Research Article

Adult Height Following Prepubertal Treatment With Antiandrogen, Aromatase Inhibitor, and Reduced Hydrocortisone in CAH

Deborah P. Merke,[1,2] Ashwini Mallappa,[1] Megan Parker,[1] Charles Sukin,[1] Sarah E. Kulkarni,[1] Margaret F. Keil,[2] Carol Van Ryzin,[1] Suvimol Chirathivat Hill,[1] James C. Reynolds,[1] Gordon B. Cutler Jr.,[2] and Ninet Sinaii[1]

[1]Department of Pediatrics, National Institutes of Health Clinical Center, Bethesda, MD 20892, USA
[2]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA

Correspondence: Deborah P. Merke, MD, MS, Department of Pediatrics, National Institutes of Health Clinical Center, Bldg. 10, Rm. 3-2750, 10 Center Drive, MSC 1932, Bethesda, MD 20892-1932, USA. Email: dmerke@nih.gov.

Abstract

Context: Height outcome in patients with classic congenital adrenal hyperplasia (CAH) is suboptimal due to glucocorticoid and androgen excess.

Methods: In an open, randomized, controlled trial, children with classic CAH were randomized to receive a combination regimen of antiandrogen, aromatase inhibitor, reduced hydrocortisone, and fludrocortisone prior to puberty or standard therapy (hydrocortisone, fludrocortisone). Females continued on antiandrogen during puberty. The primary endpoint was adult height.

Results: Of 62 children randomized, 45 completed the study. Adult height SDS did not differ between the investigational and control groups (−0.34 [0.93] vs −0.60 [0.89], respectively), mean difference 0.26 [95% CI −0.29, 0.82], $P = .35$), irrespective of midparental height, but was greater than the predicted adult height pretreatment in both groups ($P < .001$). Growth rate and rate of bone maturation were reduced in the investigational group prior to puberty, despite lower hydrocortisone dose (7.6 [1.5] vs 15.0 [3.6] mg/m^2/day, $P < .001$), and improvement in predicted adult height appeared greater at pubertal onset ($P = .049$) compared to standard therapy. Antiandrogen treatment during puberty in girls allowed for lower-dose glucocorticoid, and improved height outcome (adult minus midparental height: −0.7 [4.6] vs −5.6 [5.2] cm, mean difference 4.9 [95% CI 0.09, 9.7], $P = .046$). Those who received GnRHa had lower growth rate ($P = .023$) and longer years of unchanged bone age ($P = .017$), regardless of treatment.

Conclusion: Prepubertal antiandrogen, aromatase inhibitor combination with reduced hydrocortisone improves short-term predicted height for children with CAH but does not result in taller adult stature than those treated with standard therapy, and is not recommended. Females may benefit from antiandrogen treatment during puberty.

Key Words: congenital adrenal hyperplasia, CAH, aromatase inhibitor, antiandrogen, adult height

Abbreviations: 11OHD, 11β-hydroxylase deficiency; 21OHD, 21-hydroxylase deficiency; BMI, body mass index; CAH, congenital adrenal hyperplasia; FMPP, familial male precocious puberty; GnRHa, gonadotrophin-releasing hormone agonist; HOMA-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; MITT, modified intention-to-treat; NIH, National Institutes of Health; TART, testicular adrenal rest tumor.

Congenital adrenal hyperplasia (CAH) denotes several disorders of cortisol biosynthesis. Impaired cortisol production leads to chronic corticotropin elevation and loss of negative feedback inhibition of the hypothalamic-pituitary-adrenal axis. Corticotropin-driven adrenal androgen excess is characteristic of the virilizing forms of CAH, most commonly 21-hydroxylase deficiency (21OHD), which accounts for over 90% of cases, and 11β-hydroxylase deficiency (11OHD) (1). Androgen and estrogen excess of adrenal origin can cause rapid growth, early puberty, premature epiphyseal fusion, and adult short stature (2). The fundamental aim of standard medical therapy is twofold: to replace deficient cortisol, and if indicated aldosterone, and to control corticotropin-driven androgen excess. However, standard therapy does not affect the intrinsic adrenal abnormality, and thus the adrenal glands continue to secrete an abnormally high ratio of androgen to cortisol at any given level of adrenal activity. As a result, supraphysiological glucocorticoid doses are often necessary to control adrenal androgen production, but excess glucocorticoid suppresses growth (2).

Despite decades of study, the growth and development of most children with CAH remain suboptimal. Retrospective studies indicate that the adult height of treated CAH patients is relatively independent of the degree of adrenal androgen control, suggesting that both hyperandrogenism and hypercortisolism contribute to the observed adult short stature (3). A meta-analysis of data from 35 centers and over 1000 patients showed that classic CAH adult height SDS averaged −1.38 (10 cm below the population mean, corresponding to the 8th percentile) and −1.03 SDS (7.5 cm) below midparental

Received: 18 July 2024. **Editorial Decision:** 23 November 2024. **Corrected and Typeset:** 13 December 2024
Published by Oxford University Press on behalf of the Endocrine Society 2024.

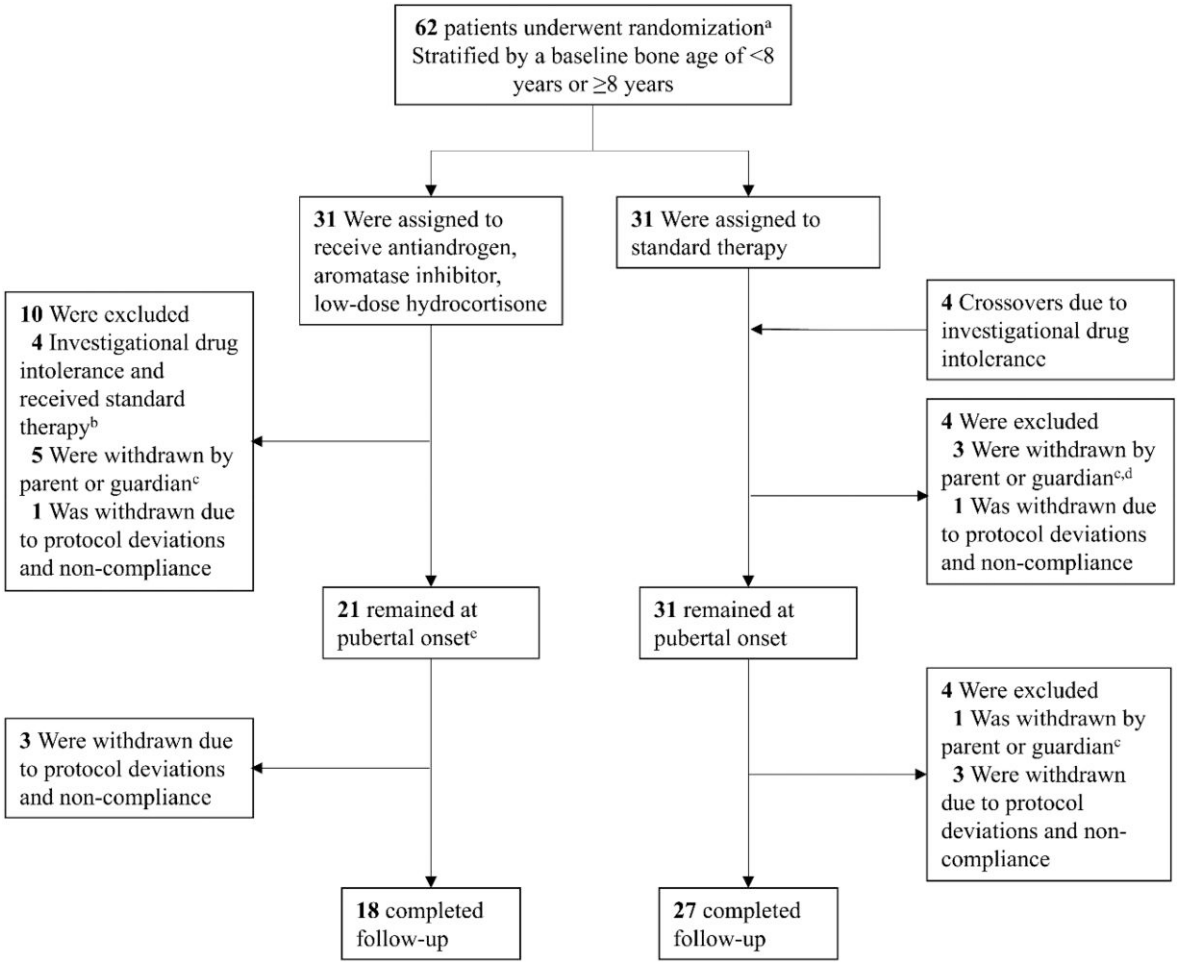

Figure 1. Flowchart showing randomization, treatment, and follow-up of modified intention-to-treat population. [a]Patients who could not tolerate investigational drugs were switched to standard therapy. Children with early puberty (girls < 9 years old; boys < 10 years old) were treated with gonadotrophin-releasing hormone agonist (GnRHa) therapy which was discontinued at age 13 in girls or age 14 in boys. [b]1 allergic reaction, 3 gastrointestinal intolerance. [c]Withdrew due to time commitment. [d]1 withdrew due to the desire to receive growth hormone therapy, a study exclusion. [e]Investigational regimen was discontinued at age 13 in girls or at age 14 in boys; girls continued antiandrogen therapy.

height, reflecting the need for alternative treatment options to optimize linear growth (4).

Whether childhood interventions that improve height predictions or normalize short-term growth rate can alter adult height has been unclear. The regimen of an antiandrogen and aromatase inhibitor in combination with reduced hydrocortisone dose was first proposed in 1990 (5), and subsequently maintained normal growth rate and skeletal maturation when given for 2 years to prepubertal children with classic CAH (6). We tested whether this prepubertal regimen would improve adult height in CAH in a long-term clinical trial.

Methods

Trial Design and Participants

We conducted an open-label, single-center, parallel group, randomized controlled trial involving children with classic CAH at the National Institutes of Health (NIH) Clinical Center, Bethesda, Maryland, USA (Clinicaltrials.gov no. NCT00001521). The trial was approved by the NIH Institutional Review Board. Written informed consent was obtained from one parent/guardian and assent was obtained for children > 7 years of age.

Boys with bone age ≤ 13 years and girls with bone age ≤ 11 years with classic 21OHD or 11OHD were eligible (Fig. 1). Bone age was determined from a radiograph of the left hand and wrist using the Bayley-Pinneau method (7). Exclusion criteria included concurrent illness requiring glucocorticoids and use of medication interfering with glucocorticoid metabolism.

Trial Procedures

Randomization was performed by the NIH Pharmacy using a table of random numbers. Patients were stratified by bone age < 8 years or ≥ 8 years. Patients were randomly assigned, in a 1:1 ratio, to receive either the investigational regimen of aromatase inhibitor (testolactone 40 mg/kg/day or letrozole 2.5 mg/day after 2004), antiandrogen (flutamide 10 mg/kg/day), reduced hydrocortisone dose (8 mg/m^2/day) approximating physiological cortisol production rates (8, 9) until age 13 years in girls or age 14 years in boys, and fludrocortisone, or the standard treatment with hydrocortisone and fludrocortisone if indicated. Over 3 weeks, doses of flutamide and aromatase inhibitor were incrementally increased, while the hydrocortisone dose was decreased. Adjustments in hydrocortisone dose were permitted while receiving standard treatment throughout the study, as would be the case in

clinical practice. While administering hydrocortisone, preferably in a dose of 10 to 15 mg/m^2/day and not exceeding 25 mg/m^2/day, the mineralocorticoid dose was adjusted as needed to maintain a normal plasma renin activity. While receiving the investigational regimen, the dosage of hydrocortisone was adjusted on an individual basis to allow for an increase for symptoms or signs of adrenal insufficiency, or for markedly elevated adrenal androgens (17-hydroxyprogesterone >10 000 ng/dL) with bone age advancement. Glucocorticoid dose was also increased to a minimum of 12 mg/m^2/day if growth of testicular adrenal rest tumor (TART) was observed on testicular ultrasound. Antiandrogen therapy was continued in girls until 2 years after menarche or when final height was reached, whichever occurred first. Children with early puberty (girls < 9 years old; boys < 10 years old) were treated with gonadotrophin-releasing hormone agonist (GnRHa) therapy which was discontinued at chronologic age 13 years in girls or 14 years in boys to allow pubertal onset within 2 SD of the general population.

Children were assessed at the National Institutes of Health Clinical Center (Bethesda, MD, USA) every 6 months until adult height was achieved. At each visit, the following were obtained: the mean of 3 morning height measurements by stadiometer, weight and pubertal stage, testicular ultrasound, bone age, routine safety laboratory measures (ie, complete blood count, electrolytes, blood urea nitrogen, creatinine, mineral panel, fasting blood glucose and insulin, hepatic panel) and hormonal biomarkers (17-hydroxyprogesterone, androstenedione, testosterone, plasma renin activity). The morning hydrocortisone dose was withheld until after these samples were obtained at approximately 08:00 hours. Early morning hormonal biomarkers prior to medication were also obtained between visits, at 3-month intervals. Bone age was determined by a single radiologist (S.C.H.) who was unaware of the patients' treatment status. At the final visit, a dual-energy x-ray absorptiometry (DEXA) scan was performed using a Hologic Densitometer QDR 4500 (Hologic, Bedford, MA).

Outcome Measures

The primary outcome was adult height expressed in standard deviation score (SDS) units relative to the general population, with attainment of adult height defined as incremental growth < 1.5 cm over 12 months. Height SDS was based on National Health and Nutrition Examination Survey data (10) and adult height SDS was based on data at 20 years old, as previously described (11). Predicted adult height at baseline was calculated using the bone age at the baseline visit or the first available bone age according to the Bayley-Pinneau method (7). Secondary outcomes were evaluated at "adult height" (final visit) and "pubertal onset," defined as when patients entered puberty (Tanner 2 breast in females, testicle size ≥ 4 mL in males) or completed therapy with either aromatase inhibitor and/or GnRHa (age 13 years in girls and 14 years in boys). Secondary outcomes were adult height in relation to midparental height, changes in predicted adult height (7), growth rate, and rate of bone maturation before puberty and during puberty until adult height, number of prepubertal years bone age remained unchanged, adrenal androgen biomarker levels, hydrocortisone dose, and cumulative glucocorticoid exposure. Exploratory outcomes evaluated body mass index (BMI) changes during the study periods, insulin resistance, age at menarche, bone mineral density, and proportion of females with normal menstrual cyclicity and males with TART at adult height. BMI percentile was calculated using US anthropometric reference data as previously described (10, 11). Insulin resistance was assessed according to the homeostasis model assessment of insulin resistance (HOMA-IR) method, as previously described (12). Menstrual cyclicity was obtained via patient report at each visit.

Patients randomized to the investigational group had intensive liver function monitoring as a precaution against flutamide-associated liver toxicity, which included biochemical testing every 2 weeks for the initial 3 months, every month for the next 9 months, and every 3 months thereafter.

Statistical Analysis

The group size required to give 80% power to detect a 5-cm difference (about 2 inches, considered clinically meaningful) using a two-sample, equal variance Student *t* test and alpha 0.05, was 24 per study arm. The final group size allowed for a 25% to 30% dropout rate.

Efficacy analyses were performed in a modified intention-to-treat (MITT) population defined by treatment received, protocol compliance, and completed follow-up, and are presented (Fig. 1). The 4 patients who did not tolerate the antiandrogen and aromatase inhibitor regimen were withdrawn from the investigational arm within 4 weeks of study onset, were followed on standard therapy to adult height, and were analyzed as treated (ie, standard therapy) in the MITT analysis (Fig. 1).

Data are reported as frequency (percentage), mean (SD), or median [interquartile range (IQR)]; differences in means, medians, or proportions are reported with their respective 95% CI. Continuous data or outcome changes during study periods were compared between treatment arms using Student *t* test or Wilcoxon rank sum test. Categorical data were compared using Fisher exact test. The primary outcome (adult height SDS units) was compared between treatment arms using the two-sample Student *t* test. Multivariable and repeated measures analyses utilized mixed effects models. Post hoc comparisons were corrected for multiplicity using the stepdown Bonferroni method. Statistical evidence was based on magnitude of differences, data variability, and *P* values. No formal interim analysis was performed as per the protocol. Statistical analyses were performed using SAS v9.4 (SAS Institute).

Results

Patients were recruited from February 1996 to April 2004. Eligibility was determined by medical record review. A total of 62 children with classic CAH 21OHD or 11OHD (39 male, 23 female) underwent randomization, with 31 assigned to each treatment arm. For the investigational arm, 4 patients did not tolerate testolactone/flutamide treatment, were crossed over to the standard arm within 4 weeks and were subsequently analyzed as treated in the standard therapy arm of the MITT analysis, presented here (Fig. 1). One child had an allergic reaction and 3 had gastrointestinal symptoms that did not resolve within the first 3 to 4 weeks of therapy. Nine other patients in the investigational arm were withdrawn from study (5 by parent or guardian and 4 by investigators for protocol deviations and noncompliance), leaving 18 investigational arm completers for the MITT analysis. For the

Table 1. Patient characteristics at baseline (modified intention-to-treat population)

Characteristic	Antiandrogen, aromatase inhibitor, reduced hydrocortisone (n = 27)	Standard therapy (n = 35)
Male sex	15 (55.6%)	23 (65.7%)
Age, years	5.6 (3.5-7.5)	5.1 (3.5-6.4)
Age at CAH diagnosis, years	0 (0-2.5)	0 (0-0.1)
CAH phenotype		
Salt-wasting 21-hydroxylase deficiency	18 (66.7%)	21 (60.0%)
Simple virilizing 21-hydroxylase deficiency	9 (33.3%)	12 (34.3%)
11β-hydroxylase deficiency	0	2 (5.7%)
Medication		
Hydrocortisone dose—mg/m^2/day	14.7 (3.8)	13.9 (3.5)
Fludrocortisone dose—mcg/day	150 (100-250)	100 (100-200)[a]
Anthropometrics		
Height (SDS)	0.9 (1.8)	0.3 (1.5)
Weight (SDS)	1.1 (1.6)	0.5 (1.5)
Body mass index (SDS)	1.0 (1.2)	0.6 (1.3)
Bone age—chronological age, years	2.9 (2.9)	2.3 (2.7)
Predicted height (SDS)[b]	−2.0 (1.5)	−2.1 (1.5)
Midparental height (SDS)[c]	0.2 (0.7)	0.2 (0.8)
Pubic hair staging		
1	14 (53.9%)	27 (77.1%)
2	6 (23.1%)	3 (8.6%)
3	5 (19.2%)	5 (14.3%)
4	1 (3.9%)	0
5	0	0
Disease-related comorbidities		
Early puberty[d]	5 (18.5%)	5 (14.3%)
Testicular adrenal rest tumor	0	2

Values are mean (SD), n (%) or median (IQR).
Abbreviations: CAH, congenital adrenal hyperplasia; SDS, standard deviation score.
[a]Excludes n = 2 with 11β-hydroxylase deficiency.
[b]Predicted height (first available) was calculated using the bone age at the baseline visit or the first available bone age, using the Bayley-Pinneau method.
[c]Midparental height was calculated using the formula: father's height (cm) + mother's height (cm)/2 ± 6.5 cm.
[d]Tanner 2 breast in females < 9 years old, testicle size ≥4 mL in males < 10 years old.

standard therapy arm, 4 patients were added early due to investigational drug intolerance, 4 were withdrawn by parent or guardian, 6 were withdrawn by investigator for protocol deviations and noncompliance, and 2 previously withdrawn patients returned for a final study visit—providing 27 completers for the MITT analysis.

Overall, the 2 groups had similar baseline characteristics; however, those in the investigational group were receiving higher doses of fludrocortisone ($P = .015$) (Table 1). The majority had advanced bone maturation at study entry (overall median 2.1 years [IQR 0.2-4.7]), and advanced bone maturation by sex was similar between treatment groups. Children were followed on average for 10.1 years (median 10.7 years [IQR 7.9-12.3], maximum 16.7) until adult height.

Adult height SDS, the primary outcome, did not differ between the investigational vs standard therapy groups (−0.34 (0.93) vs −0.60 (0.89), respectively, SDS mean difference = 0.26 [95% CI −0.29, 0.82], $P = .35$) (Table 2, Fig. 2A). The 2 treatment groups also did not differ when adult heights were adjusted for midparental height (SDS mean difference 0.38 [95% CI −0.12, 0.87], $P = .13$). In addition, sensitivity analysis of the primary outcome of adult height yielded similar conclusions in the intention-to-treat (ITT) and MITT analyses (investigational therapy vs standard therapy: ITT −0.54 (0.97) vs −0.47 (1.00), $P = 0.78$; MITT −0.34 (0.93) vs −0.60 (0.89), $P = .35$).

When adult height SDS was compared to predicted adult height at baseline, the achieved adult height SDS was greater than the baseline predicted adult height for both groups (investigational therapy: −0.34 [0.93] vs −2.06 [1.62], $P < .001$; standard therapy: −0.60 [0.89] vs −2.06 [1.60], $P < .001$).

Similar predicted height and adult height outcomes in the investigational group and the standard therapy group were observed at baseline, pubertal onset, adult height, and adult height adjusted for midparental height (Fig. 2A). However, at pubertal onset after receiving on average 7.9 (2.5) years of antiandrogen, aromatase inhibitor, and reduced hydrocortisone dosing, the improvement in predicted height from study entry to pubertal onset was greater in the investigational group compared to the standard therapy group (1.93 [1.29] vs 1.10 [1.32] SDS, mean difference 0.83 [95% CI 0.005, 1.65], $P = .049$) (Table 2, Fig. 2A).

The growth rate and rate of bone maturation from study entry to pubertal onset were lower in the investigational group compared to the standard therapy group (height velocity

Table 2. Primary and secondary end points (modified intention-to-treat population)

End point	Antiandrogen, aromatase inhibitor, reduced hydrocortisone (n = 18)[a]	Standard therapy (n = 27)[b]	Difference (95% CI)[c]	*P* value
Primary efficacy end point				
Adult height (SDS)	−0.34 (0.93)	−0.60 (0.89)	0.26 (−0.29, 0.82)	.35
Secondary efficacy end points				
Anthropometrics				
Adult height – Midparental height (SDS)	−0.45 (0.85)	−0.83 (0.78)	0.38 (−0.12, 0.87)	.13
Males	−0.89 (0.75)	−0.93 (0.78)	0.04 (−0.62, 0.69)	.91
Females	−0.02 (0.72)	−0.67 (0.79)	0.66 (−0.08, 1.39)	.078
Predicted adult height change (SDS)[d]				
Baseline to pubertal onset visit	1.93 (1.29)	1.10 (1.32)	0.83 (0.005, 1.65)	.049
Pubertal onset to final visit	−0.10 (0.66)	0.14 (0.54)	−0.25 (−0.63, 0.14)	.20
Bone age unchanged, no. of yrs				
Baseline to pubertal onset visit	3.86 (2.13)	2.78 (2.43)	1.08 (−0.37, 2.54)	.14
Pubertal onset to final visit	0.39 (0.68)	0.70 (0.73)	−0.32 (−0.75, 0.12)	.16
BMI change (SDS)				
Baseline to pubertal onset visit	0.12 (0.70)	0.36 (0.79)	−0.24 (−0.67, 0.19)	.26
Pubertal onset to final visit	0.06 (0.54)	−0.20 (0.61)	0.14 (−0.22, 0.50)	.43
BMI (SDS)				
Pubertal onset visit	1.07 (1.30)	1.09 (0.93)	−0.02 (−0.64, 0.60)	.63
Final visit	0.79 (1.13)	0.89 (0.83)	−0.10 (−0.69, 0.48)	.53
Medication				
Hydrocortisone dose, mg/m^2/day				
At pubertal onset	7.6 (1.5)	15.0 (3.6)	−7.4 (−8.9, −5.9)	<.001
At adult height	16.4 (3.1)	16.8 (2.9)	−0.4 (2.2, 1.4)	.63
Average daily dose	10.1 (1.7)	15.0 (2.4)	−4.9 (−6.2, −3.6)	<.001
Baseline to pubertal onset				
Males	9.5 (1.6)	15.0 (2.8)	−5.5 (−7.6, −3.3)	<.001
Females	9.1 (1.5)	13.9 (2.6)	−4.8 (−6.9, −2.7)	<.001
Pubertal onset to adult height				
Males	14.7 (0.9)	15.5 (2.5)	−0.8 (−2.2, 0.6)	.25
Females	9.5 (2.2)	15.5 (3.0)	−6.0 (−8.6, −3.4)	<.001
Biochemistry				
17-hydroxyprogesterone in optimal range, %, median (IQR)				
Baseline to pubertal onset	11.8 (5.9-22.7)	35.9 (19.4-65.2)	−23.2 (−43.8, −2.7)	<.001
Pubertal onset to final visit	0 (0-30.0)	28.6 (11.8-54.5)	−28.6 (−55.6, 1.5)	.026
Androstenedione in normal range, %, median (IQR)				
Baseline to pubertal onset	0 (0-10.5)	45.0 (28.6-78.6)	−45.0 (−65.1, −24.9)	<.001
Pubertal onset to final visit	20.2 (0-50.0)	50.0 (25.0-81.8)	−27.8 (−66.5, 11.0)	.035
Testosterone ng/dL, median (IQR)				
Baseline to pubertal onset	86.3 (42.2-100.0)	24.5 (19.7-36.8)	61.7 (34.4, 89.1)	<0.001
Pubertal onset to final visit				
Males	336.0 (303.3-492.5)	418.4 (349.6-504.4)	−82.4 (−250.1, 85.3)	.45
Females	42.3 (33.5-155.9)	34.4 (20.6-52.1)	4.8 (−75.5, 85.2)	.18
Disease-related comorbidities				
Onset of early puberty, no. (%)[e]	12 (75.0%)	9 (37.5%)	37.5% (5.1, 63.4)	.027
Testicular adrenal rest tumors (males), no. (%)				
Pubertal onset visit[f]	4 (33.3%)	3 (15.0%)	18.3% (−14.4, 50.1)	.38
Final visit	7 (77.8%)	7 (41.2%)	36.6% (−4.1, 67.8)	.11
Age at menarche (females), yr	14.7 (1.7)	13.6 (0.9)	1.1 (−0.2, 2.4)	.091
Normal menstrual cyclicity (females), no. (%) at final visit	4 (50.0%)	7 (70.0%)	−20.0% (−61.9, 29.7)	.63

(*continued*)

Table 2. Continued

End point	Antiandrogen, aromatase inhibitor, reduced hydrocortisone (n = 18)[a]	Standard therapy (n = 27)[b]	Difference (95% CI)[c]	*P* value
Metabolic				
HOMA-IR > 2.5, no. (%)	8 (44.4%)	12 (46.2%)	−1.7% (−31.5, 28.8)	1.0
Anterior posterior spine BMD at final visit (SDS)	−0.19 (1.28)	−0.25 (0.84)	0.06 (−0.61, 0.73)	.86
Femoral neck BMD at final visit (SDS)	−0.07 (1.23)	−0.32 (1.03)	0.26 (−0.46, 0.97)	.47

Data are mean (SD), n (%), unless otherwise specified. Reported *P* values are uncorrected for multiplicity where post hoc comparisons were carried out.
Abbreviations: BMD, bone mineral density; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance.
[a]Investigational group n = 18 at final study visit (9 male, 9 female); n = 21 at pubertal onset (12 male, 9 female).
[b]Standard therapy group n = 27 at final study visit (17 male, 10 female; 1 with 11-OH deficiency CAH); n = 31 at pubertal onset (20 male, 11 female; 2 with 11-OH deficiency CAH).
[c]For results reported as median (IQR), this is the difference in medians and 95% CI for the difference. For results reported as proportions, this is the difference between the proportions and 95% exact CI for the difference.
[d]Predicted height was calculated using the bone age at the baseline visit or the first available bone age, using the Bayley-Pinneau method.
[e]Denominators are n = 16 for investigational group and n = 24 for standard therapy who did not have early puberty at baseline.
[f]Pubertal onset visit was defined as the visit when patients entered puberty (Tanner 2 breast in females, testicle size ≥4 mL in males) or completed therapy with aromatase inhibitor and or gonadotrophin-releasing hormone agonist therapy.

−1.01 [1.84] vs −0.34 [2.18] SDS, mean difference −0.67 [95% CI −0.98, −0.36], $P < .001$; bone age advance per chronologic year 0.47 [0.33] vs 0.76 [0.48], respectively, mean difference −0.29 [95% CI −0.54, −0.05], $P = .019$) (Fig. 2B and 2C). These findings were irrespective of GnRHa therapy ($P < .001$ and $P = .035$, respectively).

Overall, GnRHa therapy for early puberty (< 10 years boys; < 9 years girls) was given to 26 patients (14 [77.8%] investigational vs 12 [44.4%] standard, difference 33.3% [95% CI 2.8, 58.3], $P = .035$). In a multivariable analysis, receiving GnRHa contributed to prepubertal lower growth rate ($P = .023$) and possibly greater predicted height change from baseline ($P = .087$) when adjusting for treatment arm. The number of years bone age remained unchanged was correlated with height gained over initial predicted height ($r_s = 0.64$, $P < .001$), and receiving GnRHa was associated with frozen bone age (4.41 [2.22] vs 2.50 [2.12] years of unchanged bone age, $P = .017$), irrespective of treatment (Fig. 3A-3C).

After discontinuation of sex steroid blockade and GnRHa therapies, height velocity SDS to adult height (final visit) was higher in the investigational group (0.65 [1.42] vs −0.29 [1.34], mean difference 0.94 [95% CI 0.64, 1.24], $P < .001$), while the annual rate of bone maturation did not differ between the 2 groups (Fig. 2B and 2C). Although adult height did not differ between the 2 groups overall, female patients receiving the investigational regimen lost the least adult height based on genetic potential; on average, they lost less than 1 cm compared to a loss of ∼5 cm in the standard therapy female group, with improved adult height (adult height minus midparental height: −0.7 [4.6] vs −5.6 [5.2] cm, mean difference 4.9 cm [95% CI 0.09, 9.7], $P = .046$). By contrast, male patients in both groups lost ∼8 cm of adult height in relation to sex-adjusted midparental height (−7.9 [5.4] vs −8.2 [5.9] cm, investigational vs standard, respectively, mean difference 0.4 cm [95% CI −4.5, 5.3], $P = .88$). GnRHa therapy did not differ between the sexes.

Patients who received the investigational therapy received notably lower doses of glucocorticoid. The average daily hydrocortisone dose in the investigational group was 7.6 (1.5) mg/m^2/day while receiving prepubertal sex steroid blockade therapy and 10.1 (1.7) mg/m^2/day average daily dose throughout the entire study. By comparison, the standard therapy groups received an average daily dose of 15.0 (3.6) mg/m^2/day prior to puberty and 15.0 (2.4) mg/m^2/day throughout the entire study (mean difference, investigational vs standard therapy, −4.9 mg/m^2/d [95% CI −6.2, −3.6], $P < .001$).

During investigational treatment, 7 (3 female, 4 male) patients received hydrocortisone doses ≥ 12 mg/m^2/day for ≥ 6 months; 3 males with TART, 1 with multiple intercurrent illnesses, 3 in response to 17-hydroxyprogesterone > 10 000 ng/dL with bone age advancement. Antiandrogen therapy during puberty allowed for lower glucocorticoid dosing in female patients relative to male patients (9.5 [2.2] vs 15.5 [3.0] mg/m^2/day, mean difference −6.0 mg/m^2/day [95% CI −8.6, −3.4], $P < .001$). As the hydrocortisone dose was reduced in the investigational group according to study design from baseline to age 13 in girls and 14 in boys, prior to puberty the investigational group had fewer number of visits with normal androstenedione (median 0% [0-10.5] vs 45.0% [28.6-78.6], difference in medians −45.0% [95% CI −65.1, −24.9], $P < .001$), and 17-hydroxyprogesterone (median 11.8% [5.9-22.7] vs 35.9% [19.4-65.2], difference in medians −23.2% [95% CI −43.8, −2.7], $P < .001$), and higher testosterone levels (median 86.3 [42.2-100.0] vs 24.5 [19.7-36.8] ng/dL, difference in medians 61.7 [95% CI 34.4, 89.1], $P < .001$), as reflected in Table 2.

There were no differences in the other secondary outcome measures, including BMI, bone mineral density, menstrual cyclicity, and the development of TART (Table 2). Moreover, at the final visit, there was no difference between the 2 treatment groups in the size of the TART present in those males who developed TART during this longitudinal study (TART volume: 0.30 ± 0.31 cm^3 in the investigational vs 0.24 ± 0.19 cm^3 in the standard groups; $P = .72$). Normal menstrual cyclicity was present in 50% females in the investigational group and 70% of females in the standard therapy group at the final visit. Insulin sensitivity, as measured by HOMA-IR was similar between the 2 groups (median 2.42 [2.12-4.82] in the investigational vs 2.29 [1.68-3.20] in the standard groups, difference in medians 0.42 [95% CI −0.98, 1.82], $P = .12$).

The overall incidence of adverse events was similar in the 2 groups (Table 3). Elevated liver enzymes, a potential effect of antiandrogen therapy, was observed in 3 patients receiving

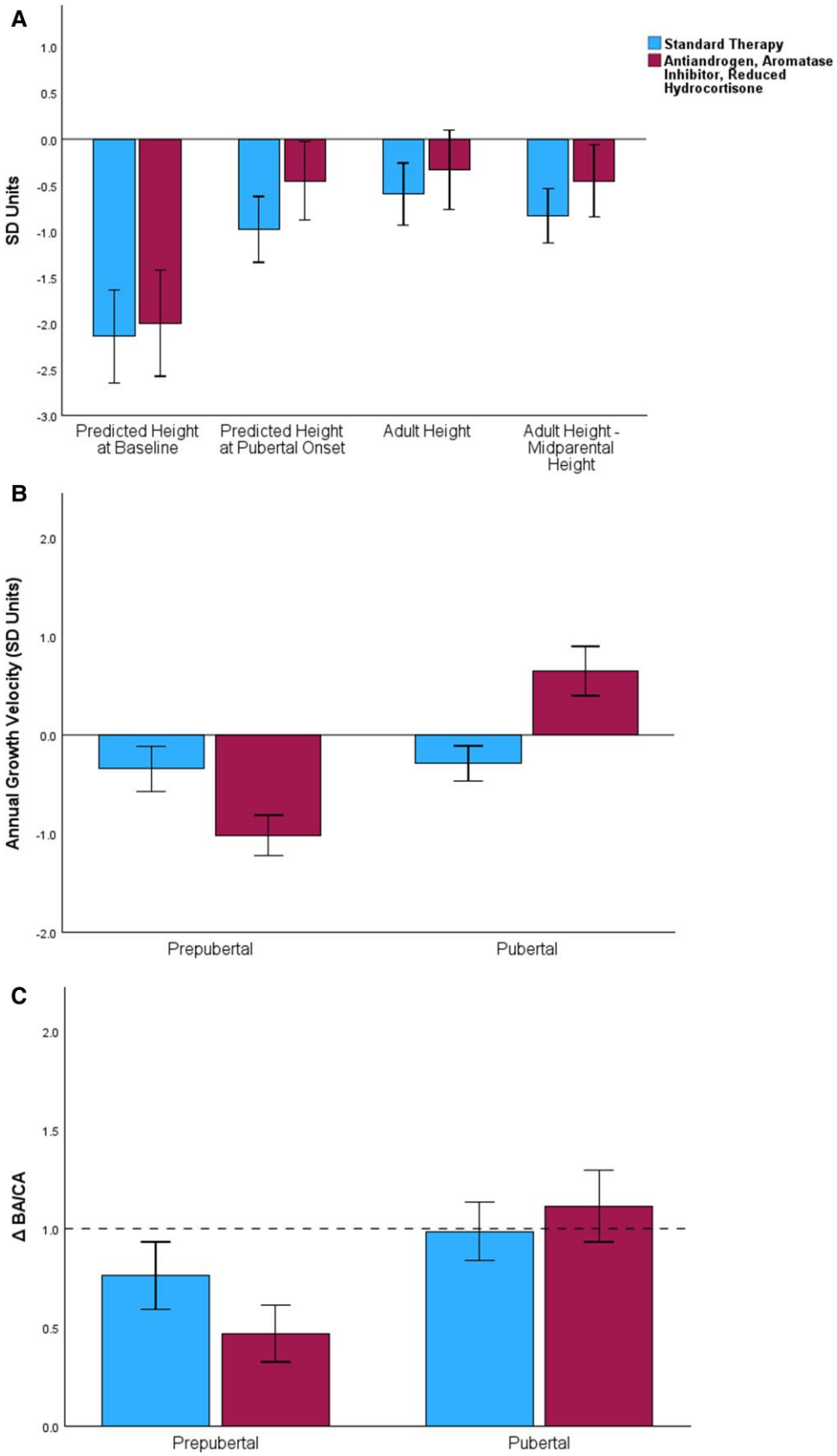

Figure 2. Primary and key secondary endpoints. Panel A shows similar predicted height and adult height outcomes in the antiandrogen, aromatase inhibitor, and reduced hydrocortisone group and the standard therapy group at baseline, pubertal onset, adult height, and adult height adjusted for midparental height. Predicted height was based on the Bayley-Pinneau method. Pubertal onset was defined as onset of Tanner 2 (breast in females, testicle size ≥ 4 mL in males) or completion of either the aromatase inhibitor and/or GnRHa (age 13 in girls and 14 in boys). Midparental height was calculated based on reported parental heights (formula: father's height (cm) + mother's height (cm)/2 ± 6.5 cm). Panel B shows differences in annual growth rate in the 2 treatment groups during prepubertal and pubertal time periods ($P < .001$). Panel C shows slower bone maturation in the antiandrogen, aromatase inhibitor, and reduced hydrocortisone group during the prepubertal time period ($P = .019$) and similar bone maturation in the 2 groups during puberty.

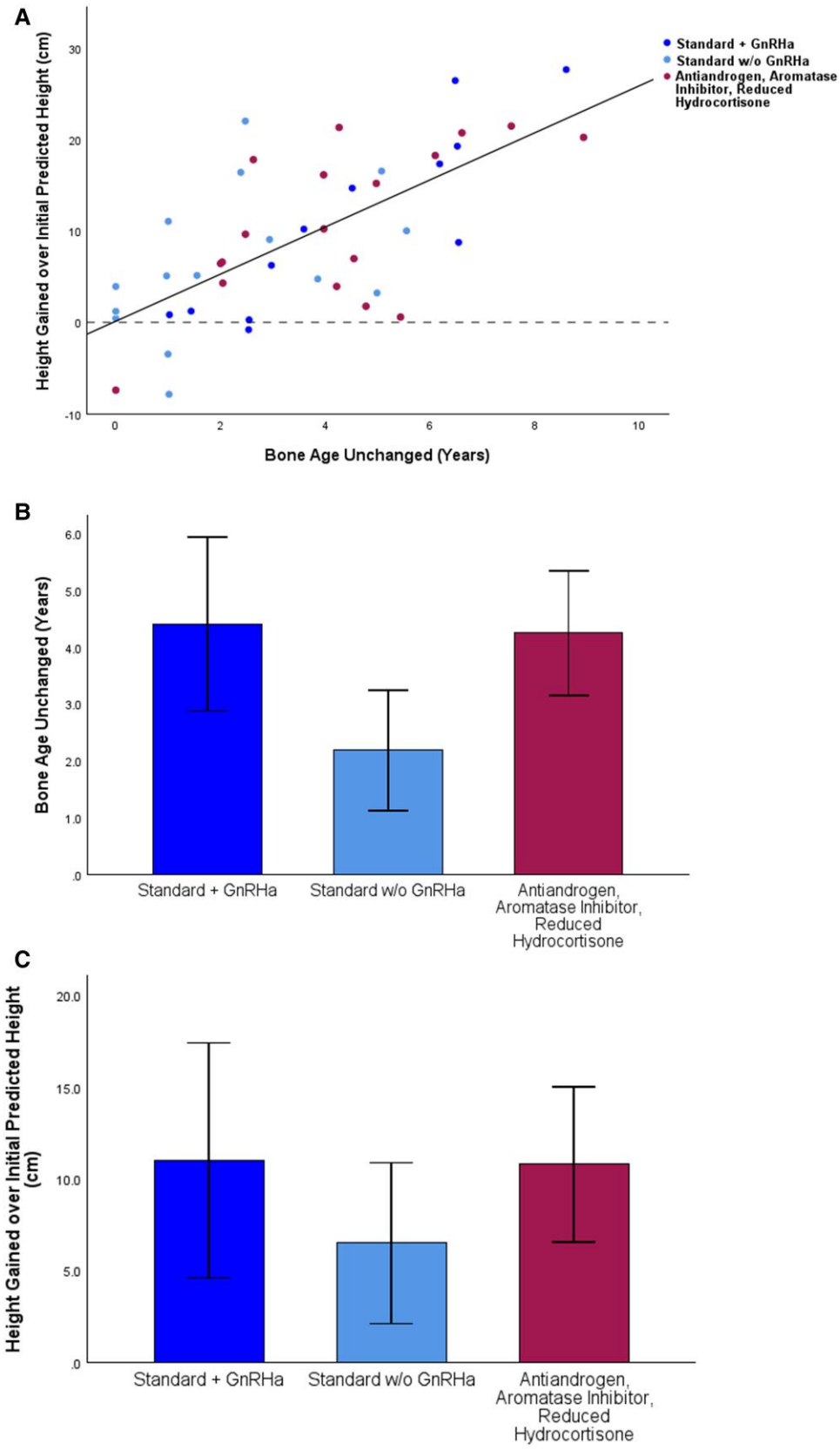

Figure 3. Interrelationship between height gained over initial predicted height, years of unchanged bone age, and use of GnRHa among patients with CAH. Means and 95% CI are shown. Predicted height was based on the Bayley-Pinneau method. Panel A shows the positive correlation between years of unchanged bone age and height gained over initial predicted height ($P < .001$), by treatment group and GnRHa therapy. Panel B shows that receiving GnRHa was associated with on average 4.4 years of unchanged bone age in the standard therapy group, similar to years of unchanged bone age in the investigational group receiving an antiandrogen, aromatase inhibitor, and reduced hydrocortisone. Panel C shows that the height gained over the initial predicted height at study entry was similar in the treatment groups, and most similar in those receiving standard therapy with GnRHa compared to the investigational group receiving an antiandrogen, aromatase inhibitor, and reduced hydrocortisone.

Table 3. Adverse events

Event[a]	Antiandrogen, aromatase inhibitor, reduced hydrocortisone (n = 31)	Standard therapy (n = 31)
Adverse events that led to discontinuation of antiandrogen and aromatase inhibitor[b]	4 (12.9%)	0
Adverse event that led to discontinuation of GnRHa	0	1 (3.23%)
Hepatobiliary	3 (9.68%)	1 (3.23%)
Gastrointestinal	9 (29.0%)	0
Musculoskeletal	5 (16.1%)	0
Skin—urticarial rash	1 (3.23%)	0
Skin—abscess	0	1 (3.23%)[α]
Somnambulism	0	1 (3.23%)[α]
Adverse events of special interest[c]	**(n = 27)**	**(n = 35)**
Glucocorticoid stress dosing	27 (100.0%)	35 (100.0%)
Days of stress dosing per year	2.94 (3.49)	2.40 (1.06)
Illnesses per year	1.69 (1.99)	1.44 (0.67)
Emergency room visit[d]	13 (48.1%)	14 (40.0%)
Emergency room visits per year	0.10 (0.19)	0.08 (0.13)
Hospitalizations	7 (25.9%)	11 (31.4%)
Hospitalizations per year	0.07 (0.19)	0.07 (0.16)

Data are mean (SD), or n (%).
[a]Shown are adverse events attributed as possibly, probably or definitely related to the investigational therapy or the GnRHa by the trial investigator. This analysis was performed in all patients randomized.
[b]One with urticarial rash one hour after receiving investigational therapy, 3 with persistent (>one week) gastrointestinal upset following initiation of aromatase inhibitor and antiandrogen therapy.
[c]This analysis was performed according to treatment received (modified intention-to-treat population).
[d]Related to adrenal insufficiency, requiring administration of intravenous hydrocortisone.

antiandrogen and 1 patient receiving standard therapy, resolved with time, with 3 patients testing positive for viral infections. Glucocorticoid stress dosing for illnesses or potential adrenal crises was similar between the 2 groups.

Female patients in the investigational group developed minimal or no axillary and pubic hair during puberty while receiving antiandrogen therapy; breast development in both study arms progressed normally through the 5 stages described by Tanner. Female patients receiving standard therapy developed the expected amount of sexual hair.

Discussion

This is the first randomized controlled trial with adult height outcome data of height-enhancing therapy for children with classic CAH. Patients who received prepubertal aromatase inhibitor, antiandrogen, and reduced hydrocortisone dose experienced slowing of bone maturation, progressive increase of predicted adult height, and greater improvement in adult height predictions at pubertal onset compared to standard therapy. However, pubertal height gain accounts for approximately 20% of adult height in healthy individuals (13, 14), is influenced by many factors, and ultimately this prepubertal investigational therapy did not significantly improve the patients' adult height compared to standard therapy.

Height outcome in classic CAH is often adversely affected due to both disease-related and treatment-related factors (2). The growth suppressive effect of glucocorticoid therapy is dose dependent and is observed especially when doses exceed 15 to 20 mg/m^2/day during puberty (15, 16). However, all patients in this study had daily hydrocortisone doses < 18 mg/m^2/day. Although glucocorticoid dose was lower throughout the prepubertal years for both sexes in the investigational therapy group, during puberty the glucocorticoid dose for male patients was similar between the 2 groups at ~15 mg/m^2. By contrast, according to study design, the female patients in the investigational group continued antiandrogen therapy until 2 years postmenarche or adult height, which allowed the mean glucocorticoid dose of 9.5 mg/m^2/day during the pubertal years to remain within the physiologic range of normal cortisol production rate (~4-12 mg/m^2/d in oral hydrocortisone dose-equivalents) (8, 9, 17). This sex difference in pubertal hydrocortisone dose likely contributed to the better adult height outcome in female compared to male participants. Although aromatization of androgens to estrogens is thought to be the major factor in pubertal growth acceleration and epiphyseal fusion (18), we cannot exclude antiandrogen therapy during puberty as a possible factor. Unlike males, females in the investigational treatment group achieved adult heights approximating their genetic potential, and the positive difference in midparental height – adjusted adult height compared to females in the standard therapy group, while not statistically significant ($P = .078$), approached the level that patients consider meaningful (+0.66 SDS [4.25 cm]).

Perturbations of growth and puberty are common complications observed in children with classic CAH, especially those who are not diagnosed and treated early. This long-term study started in 1996, thus not all children were born in states with neonatal screening for CAH. Patients in both groups had advanced skeletal age (median advancement 2.1 years) with poor predicted adult height at study entry. Although advanced bone maturation early in life is expected to impact adult height with loss of epiphyseal growth potential (19, 20), both groups achieved improved height outcomes compared to predictions at study entry and both achieved adult height within 1 SD of the population norm. GnRHa therapy was offered to both treatment groups for early central puberty and was given to 44% of those in the standard therapy group. GnRHa therapy has been shown to increase adult height in children with GnRH-dependent precocious puberty (21) and in adolescents with idiopathic short stature with normally timed puberty (22). We chose to initiate GnRHa therapy at 9 years old for girls and 10 years old for boys to standardize its effect in both groups, recognizing that this is one year older than the standard definition of central precocious puberty. GnRHa therapy effectively prevented bone age advancement in both groups and likely contributed to the lack of difference between the 2 groups in adult height. Other potential contributing factors were close patient follow-up with frequent biochemical monitoring/dose titration, hydrocortisone dosing < 18 mg/m^2/day during puberty in both groups, and improved compliance in the clinical trial setting (Hawthorne effect). Each of these factors may have contributed to the improved adult height of the standard therapy group vs a published meta-analysis of adult CAH height (−0.60 vs −1.38 SDS, respectively) (4).

Early central puberty—a frequent occurrence in CAH—was observed with similar frequency in both groups at baseline (14%-19%). Unexpectedly, however, a significantly greater frequency of early puberty and GnRHa therapy occurred in the investigational vs the standard therapy group (78% vs 44%). Possible explanations for more frequent early puberty in the investigational group include randomization imbalances in the predestined pubertal timing, dropout imbalances in pubertal timing, or lower prepubertal hydrocortisone dose in the investigational arm. Our study does not permit distinction among these and other possibilities.

Our hypothesis to improve treatment of children with CAH with antiandrogen and aromatase inhibitor treatment arose from prior study of boys with familial male precocious puberty (FMPP). Accelerated growth rate and bone maturation of these boys was controlled effectively with an antiandrogen (spironolactone) and an aromatase inhibitor (primarily testolactone and later anastrozole) (23). We hypothesized that a similar approach would be effective in CAH, and would allow us to avoid the complications of glucocorticoid excess by reducing hydrocortisone dose to physiologic levels. Since patients with classic CAH have a defect in aldosterone production, we substituted flutamide for spironolactone due to the latter's mineralocorticoid antagonist activity. Unlike boys with FMPP, who attained a midparental height-adjusted adult height SDS of −0.45, boys with CAH in the investigational group had midparental height-adjusted adult height SDS of −0.89. Possible explanations for this difference include supraphysiologic glucocorticoid dosing during early childhood or puberty in the boys with CAH, differences in the drug combinations used, and potential differences in gonadal and adrenal androgens and estrogens—and hypothalamic-pituitary factors—between the 2 disorders. In our study, no prepubertal sex differences were found in growth rates or GnRHa therapy, suggesting that the supraphysiologic glucocorticoid dosage during male puberty, which is known to exert a direct, inhibitory effect on the growth plate (24), seems the most likely explanation for the sex difference in adult height outcome.

Central puberty is initiated in the brain, with well-known external influences on its timing, including exposure to sex steroids and nutritional status. Our findings of a higher rate of early puberty in the investigational arm was surprising. Higher exposure to adrenal androgens and their multiple metabolites or to corticotropin and POMC products may have played a role, but the combination of an antiandrogen that blocks at the androgen receptor and an aromatase inhibitor that blocks the conversion of androgen to estrogen was expected to normalize growth and bone maturation sufficiently to prevent early puberty. As in the current study, GnRHa therapy was also often added—due to early central puberty—to the combined regimen of an antiandrogen and aromatase inhibitor in many boys with FMPP (25). This suggests that the antiandrogen/aromatase inhibitor regimen may not have begun early enough or achieved a sufficient blockade to prevent the early onset of central puberty. In 3 children with CAH who had extremely elevated adrenal androgens and concomitant bone age advancement despite antiandrogen and aromatase inhibitor treatment, an increase in hydrocortisone dose to ~12 mg/m^2/day achieved improved control. Thus, incomplete blockade appeared to occur, but in a minority of patients.

When the current study was conceived in the early 1990s, testolactone was the sole aromatase inhibitor considered sufficiently safe for a long-term study in children. However, the need for large testolactone doses at thrice-daily intervals, and gastrointestinal intolerance in a minority of patients, made this approach unwieldy for wider use. However, we undertook this study for "proof of concept," knowing that more potent aromatase inhibitors and antiandrogens were in development. Today, this same conceptual approach could be undertaken with 2 additional pills daily administered with the existing thrice-daily hydrocortisone doses. Despite lack of clinical trials, aromatase inhibitors are commonly used in children with CAH. In our view, the key argument against this approach is that it failed to significantly improve adult height outcome, and that theoretically more appealing add-on therapies appear likely to become available (26-28).

Owing to the central role of estrogens in skeletal maturation and epiphyseal fusion, off-label use of aromatase inhibitors has gained popularity as an adjuvant height-enhancing agent in children with hyperandrogenic or hyperestrogenic states, idiopathic short stature, and in male pubertal delay (29, 30). However, in this first randomized controlled clinical trial to adult height with aromatase inhibitor therapy in CAH, the short-term improvement in predicted adult height did not achieve a significant adult height gain compared to standard therapy. Thus, our findings do not support the use of aromatase inhibitors as height-enhancing therapy for patients with CAH. However, we cannot exclude the possibility that a more potent aromatase inhibitor/antiandrogen combination, with continued aromatase inhibitor during male puberty and continued antiandrogen during female puberty, may yield better results than our initial approach.

Our study also provides evidence that physiologic glucocorticoid replacement (approximately 8 mg/m^2/day of hydrocortisone) is safe in growing children and even moderate glucocorticoid dosing may play a role in growth suppression during puberty. Studies have suggested that lower-dose hydrocortisone might increase risk of adrenal crisis in children (31), but we found no differences in illness and hospitalization rates between the 2 treatment groups. Moreover, differences in disease-related TART formation (males) and irregular menses (females) associated with excess corticotropin and elevated adrenal-derived androgens respectively were not observed. Overall, the prevalence of TART among our patients was as expected based on prior reports of TART prevalence (32), suggesting that lower-dose glucocorticoid therapy during the prepubertal years does not significantly increase risk of TART formation. However, once TART developed, 3 males in the investigational group were treated with ~12 mg/m^2/day because of concern of possible TART progression.

Antiandrogen therapy in the females with CAH during puberty had the advantage of enabling a continued physiologic dose of glucocorticoid during puberty and may have accounted for their achievement of normal adult height in relation to midparental height. Although we are encouraged by this finding, our study began long ago and was not designed to permit a current assessment of potential positive or negative reproductive effects of antiandrogen during female puberty. Because exposure to high androgen levels is a known contributor to ovarian dysfunction and menstrual irregularities, we believe this approach deserves further investigation. The decreased sexual hair growth in the adolescent girls receiving antiandrogen was seen as a benefit to some, and none expressed dissatisfaction.

In addition to impairing childhood growth, iatrogenic hypercortisolism can decrease bone mineral density, alter metabolism, and increase the prevalence of cardiovascular disease risk factors. Children with classic CAH have higher prevalence of obesity and insulin resistance compared to the general population (12), possibly due to chronic supraphysiologic glucocorticoid dose. However, in our study, approximately 8 years of near physiologic hydrocortisone dosing during childhood did not result in decreases in BMI or insulin resistance. Differences in bone mineral density also were not observed. Our inability to mimic the circadian and ultradian rhythm of cortisol with the available methods of glucocorticoid replacement and the limited number of years patients received physiologic dosing may have played a role. Ultimately, lower-dose physiologic individualized glucocorticoid therapy is needed throughout the lifetime. New treatment approaches that aim to optimize glucocorticoid dose while maintaining adrenal androgen control include a modified-release form of hydrocortisone, approved in 2021 in the UK and Europe for patients with CAH age 12 years and older (33), and an oral corticotropin-releasing factor type 1 receptor (CRF_1) antagonist (26, 27). Studies of these promising new treatment approaches have not yet included the evaluation of growth in children, a challenging issue that has lifelong consequences.

Overall, the combination of antiandrogen, aromatase inhibitor therapy, and low-dose hydrocortisone was well tolerated. The major strengths of the study include robustness of the trial design given the randomized, longitudinal nature of the study, extensive clinical monitoring, long-term follow-up, and the rare ability to assess final height outcomes in a cohort of CAH patients.

Our study has limitations. The study was open-label, as conducting a placebo-controlled double-blind trial with multiple medications administered multiple times daily was not thought to be feasible. Dropouts were seen in both treatment groups related mostly to parent/guardian decision due to time commitment. The greater dropout rate in the investigational arm (13% due to intolerance to testolactone/flutamide) further reduced study investigational arm completers (18 vs the intended 24), thus reducing statistical power to detect a 5-cm adult height difference. Nevertheless, dropouts are often unavoidable in the ethical conduct of an intensive long-term, pediatric study. Because the primary outcome for this study was adult height after patients were treated for many years, a formal intention-to-treat (ITT) analysis was not considered clinically meaningful. GnRHa to suppress early central puberty was a confounding factor when evaluating the effects of aromatase inhibitor, antiandrogen, and reduced hydrocortisone on adult height, but restricting its use to one group was considered impractical given its FDA approval for early central puberty. Because we elected to discontinue aromatase inhibitor during the pubertal years in males, while continuing antiandrogen therapy in the females, we cannot exclude the possibility that continued aromatase inhibitor in males might have prevented the pubertal rise in hydrocortisone dose, and the reduced adult height SDS, that was observed in males compared to females. The study initially used first-generation testolactone, a steroidal aromatase inhibitor administered multiple times/day, and letrozole—a more potent, once-daily, third generation non-steroidal aromatase inhibitor—was introduced starting in 2004 (34).

We conclude that prepubertal sex steroid blockade and reduced hydrocortisone therapy may be effective in increasing adult height in CAH but is no more effective than careful monitoring with standard therapy, judicious use of glucocorticoid, and GnRHa therapy for early central puberty. Thus, this treatment regimen is not recommended, but we recommend that GnRHa therapy should be considered in shorter children with CAH and early puberty. Antiandrogen therapy during puberty in females with CAH may allow for lower pubertal glucocorticoid dosing and improve height outcomes. This study provides the only long-term clinical trial data of height-enhancing therapy in classic CAH and confirms the importance of pubertal height gain in determining adult height.

Funding

This research was supported by the Intramural Research Program of the National Institutes of Health.

Disclosures

D.P.M. received unrelated research funds from Diurnal Limited, Neurocrine Biosciences, and Adrenas Therapeutics, all through the National Institutes of Health Cooperative Research and Development Agreements. A.M. is currently employed by AstraZeneca. G.B.C. has consulting agreements with Neurocrine Biosciences. All other authors report no potential conflicts of interest in this work.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Clinical Trial Information

ClinicalTrials.gov Registration Number NCT00001521.

References

1. El-Maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. *Lancet*. 2017;390(10108):2194-2210.
2. Merke DP, Auchus RJ. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *N Engl J Med*. 2020;383(13):1248-1261.
3. Claahsen-van der Grinten HL, Speiser PW, Ahmed SF, *et al*. Congenital adrenal hyperplasia-current insights in pathophysiology, diagnostics, and management. *Endocr Rev*. 2022;43(1):91-159.
4. Muthusamy K, Elamin MB, Smushkin G, *et al*. Clinical review: adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis. *J Clin Endocrinol Metab*. 2010;95(9):4161-4172.
5. Cutler GB Jr, Laue L. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *N Engl J Med*. 1990;323(26):1806-1813.
6. Merke DP, Keil MF, Jones JV, Fields J, Hill S, Cutler GB Jr. Flutamide, testolactone, and reduced hydrocortisone dose maintain normal growth velocity and bone maturation despite elevated androgen levels in children with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2000;85(3):1114-1120.
7. Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. 2nd ed. Stanford University Press; 1959.
8. Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. *J Pediatr*. 1990;117(6):892-896.

9. Esteban NV, Loughlin T, Yergey AL, *et al*. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab*. 1991;72(1):39-45.
10. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. US Department of Health and Human Services, Centers for Disease Control and Prevention. 2009-2010. Accessed November 12, 2024. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2009
11. Finkielstain GP, Kim MS, Sinaii N, *et al*. Clinical characteristics of a cohort of 244 patients with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438.
12. Torky A, Sinaii N, Jha S, *et al*. Cardiovascular disease risk factors and metabolic morbidity in a longitudinal study of congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2021;106(12):e5247-e5257.
13. Thissen D, Bock D, Wainer H, Roche AF. Individual growth in stature: a comparison of four growth studies in the U.S.A. *Ann Hum Biol*. 1976;3(6):529-542.
14. Abbassi V. Growth and normal puberty. *Pediatrics*. 1998;102(Suppl 3):507-511.
15. Balsamo A, Cicognani A, Baldazzi L, *et al*. CYP21 genotype, adult height, and pubertal development in 55 patients treated for 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2003;88(12):5680-5688.
16. Bonfig W, Pozza SB, Schmidt H, Pagel P, Knorr D, Schwarz HP. Hydrocortisone dosing during puberty in patients with classical congenital adrenal hyperplasia: an evidence-based recommendation. *J Clin Endocrinol Metab*. 2009;94(10):3882-3888.
17. Charmandari E, Johnston A, Brook CG, Hindmarsh PC. Bioavailability of oral hydrocortisone in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Endocrinol*. 2001;169(1):65-70.
18. Karimian E, Chagin AS, Sävendahl L. Genetic regulation of the growth plate. *Front Endocrinol (Lausanne)*. 2011;2:113.
19. Speiser PW, Arlt W, Auchus RJ, *et al*. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.
20. Eugster EA, Dimeglio LA, Wright JC, Freidenberg GR, Seshadri R, Pescovitz OH. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. *J Pediatr*. 2001;138(1):26-32.
21. Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. *J Clin Endocrinol Metab*. 2008;93(1):190-195.
22. Yanovski JA, Rose SR, Municchi G, *et al*. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *N Engl J Med*. 2003;348(10):908-917.
23. Laue L, Kenigsberg D, Pescovitz OH, *et al*. Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med*. 1989;320(8):496-502.
24. Lui JC, Baron J. Effects of glucocorticoids on the growth plate. In: Ghizzoni L, Cappa M, Chrousos GP, Loche S, Maghnie M, eds. *Pediatric Adrenal Diseases. Endocrine Development: Workshop, Turin, May 2010*. Karger; 2010:187-193
25. Leschek EW, Flor AC, Bryant JC, Jones JV, Barnes KM, Cutler GB Jr. Effect of antiandrogen, aromatase inhibitor, and gonadotropin-releasing hormone analog on adult height in familial male precocious puberty. *J Pediatr*. 2017;190:229-235.
26. Sarafoglou K, Kim MS, Lodish M, *et al*. Phase 3 trial of crinecerfont in pediatric congenital adrenal hyperplasia. *N Engl J Med*. 2024;391(6):493-503.
27. Auchus RJ, Hamidi O, Pivonello R, *et al*. Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. *N Engl J Med*. 2024;391(6):504-514.
28. Mallappa A, Merke DP. Management challenges and therapeutic advances in congenital adrenal hyperplasia. *Nat Rev Endocrinol*. 2022;18(6):337-352.
29. Carani C, Qin K, Simoni M, *et al*. Effect of testosterone and estradiol in a man with aromatase deficiency. *N Engl J Med*. 1997;337(2):91-95.
30. Hero M. Aromatase inhibitors in the treatment of short stature. *Endocr Dev*. 2016;30:130-140.
31. El-Maouche D, Hargreaves CJ, Sinaii N, Mallappa A, Veeraraghavan P, Merke DP. Longitudinal assessment of illnesses, stress dosing, and illness sequelae in patients with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2018;103(6):2336-2345.
32. Claahsen-van der Grinten HL, Dehzad F, Kamphuis-van Ulzen K, de Korte CL. Increased prevalence of testicular adrenal rest tumours during adolescence in congenital adrenal hyperplasia. *Horm Res Paediatr*. 2014;82(4):238-244.
33. Merke DP, Mallappa A, Arlt W, *et al*. Modified-release hydrocortisone in congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2021;106(5):e2063-e2077.
34. Wit JM, Hero M, Nunez SB. Aromatase inhibitors in pediatrics. *Nat Rev Endocrinol*. 2012;8(3):135-147.