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Histrelin Implantation and Growth Outcomes in Children With Congenital Adrenal Hyperplasia: An Institutional Experience

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Background: Children with congenital adrenal hyperplasia (CAH) because of 21 hydroxylase deficiency (21OHD) are at risk for early or precocious puberty and a short adult height compared to population means and midparental height. The effect of histrelin in suppressing puberty and improving growth in these children has not been reported.

Methods: Retrospective cohort analysis of all patients (age ≤ 20) at our institution who underwent histrelin implantation between 2008 and 2017. Treated patients with CAH (classic and nonclassic forms of 21OHD) were identified and their growth data analyzed.

Results: Fifteen children with CAH were treated with histrelin for a median of 3 years (range 2–5; age at first implantation 7.7 ± 1.5 years). Bone age (BA) to chronologic age (CA) decreased from 1.57 ± 0.4 to 1.25 ± 0.25 ($P < .01$), while predicted adult height (PAH) increased by 7.1 ± 6.6 cm ($P < .01$). A subgroup of 10 children reached adult height. Similar changes in BA/CA and PAH were observed with therapy ($P = .02$). Adult height z improved compared to pretreatment PAH z (–1.42 ± 0.9 vs. –1.96 ± 1.1 respectively, $P < .01$), but remained lower than midparental height z ($P = .01$).

Conclusion: In this retrospective cohort study of children with CAH due to 21OHD and early or precocious puberty, histrelin implantation resulted in a decrease in BA progression compared to CA and an improvement in PAH. In the subgroup who completed growth, adult height remained significantly lower than midparental. These results need to be confirmed with prospective controlled studies.

Key Words: CAH, histrelin, leuprolide, final height, puberty

21 hydroxylase deficiency (21OHD) is the most common type of congenital adrenal hyperplasia (CAH) (1, 2). 21 hydroxylase is an enzyme within the pathway of cortisol and aldosterone biosynthesis. Lack or reduced activity of the enzyme results in cortisol deficiency, increased secretion of adrenocorticotropic hormone and subsequent adrenal androgen overproduction. Based on the severity of the enzymatic defect, the disease presents in 3 forms: the salt wasting (sw) type, which is characterized by combined aldosterone and cortisol

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deficiencies, the simple virilizing type, which presents only with cortisol deficiency, and the nonclassic form. The latter is associated with normal cortisol and aldosterone secretion, but the affected individual continues to manifest adrenal androgen hypersecretion (1). The traditional therapy for CAH is cortisol replacement, which is combined with aldosterone replacement in case of an additional mineralocorticoid defect. Cortisol therapy in CAH also suppresses the increased adrenocorticotropic hormone secretion and improves the hyperandrogenemia of the disease (1, 2).

Children with CAH due to 21OHD are at risk for premature adrenarche as well as early or precocious central puberty (1, 3). In addition, they may manifest tall stature, which can be the result of adrenal hyperandrogenemia and/or central precocious puberty (CPP). Despite their tall stature, these children experience advanced epiphyseal maturation and typically complete their growth at a younger age compared to their peers. As a result, their adult height is frequently below their genetic potential and may fall below the normal range for the general population (1, 3–5). According to a recent meta-analysis, individuals with CAH as a group have a low mean adult height at –1.38 standard deviation (SD) and a difference from midparental height of –1.03 SD.

Depot leuprolide acetate and other gonadotropin-releasing hormone (GnRH) analogues (GnRHa) have been used successfully for the treatment of CPP in the general population (6). In addition to halting the progression of puberty, these medications aim to improve growth and adult height (6). The efficacy of such therapy in children with CAH due to 21OHD is limited (7–11). Two retrospective studies in CAH observed that leuprolide administration as a single agent improved predicted adult height (PAH) (9, 10). In a prospective study, leuprolide therapy combined with growth hormone resulted in an improvement in adult height compared to matched untreated historical controls (12–14). Histrerin, a recently introduced GnRHa, has been shown to successfully suppress puberty and improve PAH in children with CPP (14). The effects of histrelin in suppressing puberty and improving growth and final height in CAH have not been reported. In this manuscript, we present our institution's experience with histrelin implantation in children with CAH caused by 21OHD.

1. Methods

A. *Study population and design*

We performed a retrospective cohort study including all patients (age ≤ 20) at our institution, who underwent histrelin implantation between January 1, 2008 and December 31, 2017. We identified 377 patients who underwent 866 unique histrelin procedures: implant insertion, removal or replacement. Data from this review has been previously reported, with a focus on the procedure technique, safety, and clinical management practices (15). Growth data were not described. From this cohort, we identified 15 patients with CAH to be included in this subanalysis. We reviewed each chart for patient demographics (age, gender) and clinical data (heights, weights, body mass index [BMI], midparental height and final height, bone ages [BAs], tanner stages, medications, and other comorbidities) from clinic visits, operative/procedure reports, telephone encounters, and all other correspondence documented in the electronic medical record. All histrelin procedures from this cohort were included up to May 2019. The review was first performed by 2 investigators (RS and BC), and then data were verified by the principal investigator (MV). All clinical data were captured within 3 months of histrelin implantation, removal or replacement.

CPP was defined as Tanner II or greater breast development in females younger than 8 years of age or testicular enlargement greater than 4 cc in males younger than 9 years of age with documented pubertal luteinizing hormone (LH) levels at baseline (LH ≥ 0.3 IU/L) or with a GnRHa stimulated LH peak of greater than 5 IU/L (16). Early puberty was defined as onset of central puberty between 8 and 9 years for females and between 9 and 10 years for males. Tanner staging was assessed according to the method of Marshall

and Tanner (17). BA and height predictions were estimated by the method of Greulich and Pyle (18). The primary investigator (MV) reviewed and read all BAs of the study. All subjects, including those with nonclassic CAH, were treated with hydrocortisone as glucocorticoid replacement. The dose was expressed as mg/m^2/day and recorded at each patient visit. The average dose per year was then calculated and reported. Subjects with sw CAH were receiving additional mineralocorticoid replacement. To assess adrenal control, data on serum 17-hydroxyprogestorone and androstendione concentrations at each patient visit were collected. The mean value per year and ranges were calculated and reported. 17-hydroxyprogestorone and androstendione measurements were obtained in the morning before hydrocortisone administration. GnRHa therapy was offered to all children with CPP. Pubertal suppression was also discussed in children with early puberty and an expected poor growth outcome, that is, PAH z ≤ –2 or height deficit z ≤ –2. Height deficit was defined as the difference between midparental height and PAH.

B. *Statistical analysis*

We used STATA 14.2 (StataCorp, College Station, TX, US) to perform all statistical analyses. Descriptive statistics are presented as means (SD) and medians (range) as appropriate. Height, weight, BMI, midparental height, and height predictions of adult height are expressed as standard deviations or z scores for age and gender as our cohort includes both males and females. Students' paired *t* tests were used to compare changes in height, weight, BMI z score, BA to chronological age (CA) ratio, and height deficit. Analysis of variance was used to compare changes in weight, height, and BMI to final height. The Kruskal–Wallis rank test was performed to assess differences in growth velocities across years. Statistical significance was set a priori ($\alpha = .05$). This study protocol was approved by the Institutional Review Board at the Children's Hospital of Philadelphia (IRB #16-012703).

2. Results

A. *Subject characteristics*

Of the 15 patients with CAH, there were 7 males and 8 females. Eight had sw CAH, 3 had simple virilizing CAH, and 4 had nonclassic CAH. Mean age of onset of puberty was 7.36 years (range 5.2–10 years). First histrelin implantation occurred at a mean age of 7.7 ± 1.5 years (range 5.35–10.5), median length of therapy was 3 years (range 2–5), and mean age at the completion of therapy was 11 ± 1.65 years (range 7.4–13.5). Four children (all males) received concomitant therapy with an aromatase inhibitor. No subject received other concomitant medication that may have affected growth. Thirteen subjects completed histrelin treatment; 10 of them have reached final height, while 3 are still growing. The remaining 2 subjects (both males) were still on histrelin at the time of this analysis.

B. *Effect of histrelin on puberty*

All subjects had signs of adrenarche at the first histrelin implantation (Tanner stages varied from 2–4). They all demonstrated early signs of central puberty (all females had breast development Tanner 2 and males had testicular enlargement from 4–10 mL). Puberty was biochemically confirmed with gonadotropin measurements in the pubertal range at baseline or after a leuprolide stimulation test (data not shown).

Histrelin clinically suppressed pubertal progression. After removing the last histrelin implant, puberty recovered within a year. Menarche was reached at 11 ± 1.78 months after the

last implant removal (mean ± SD; range 6–17 months) at the mean age of 12.6 ± 0.32 years (range 11–13).

C. *Effect on growth*

Children with CAH had tall stature with a height z = 1.15 ± 1.4 at the time of first implantation (Table 1). The mean weight and BMI z scores were 1.5 ± 0.9 and 1.45 ± 0.7, respectively. At the end of treatment, the height z had significantly decreased from baseline to 0.45 ± 1.17 ($P < .01$). Consistent with the decrease in height z scores, height velocity also decreased over the course of therapy (annual growth velocity (cm/year) was 1: 6 ± 2.5 in year 1, 4.7 ± 1.9 in year 2 and 3.2 ± 1.4 in year 3; p = 0.004) (Figure 1). Weight and BMI z scores were not different at 1.3 ± 0.7 and 1.5 ± 0.5, respectively (Table 1). Because a previous study in CAH had suggested an inverse relationship between BA at initiation of GnRHa and growth velocity during treatment (10), we explored similar associations in our cohort and found no significant results.

At the beginning of treatment, participants had a mean BA/CA ratio of 1.57 ± 0.4, indicating that BA was advanced compared to CA. At the end of therapy, the BA/CA ratio had decreased to 1.25 ± 0.25 ($P = .01$), indicating that histrelin was effective in slowing down BA progression (Table 1).

PAH for each subject was calculated at the beginning and end of histrelin therapy. PAH increased during the course of treatment by a mean of 7.1 ± 6.6 cm, suggesting a beneficial effect of histrelin on growth. Since our cohort includes both males and females, we also present the PAH as z scores. PAH z improved over the course of histrelin treatment from –2.33 ± 1.2 to –1.35 ± 1.5 ($P = .02$). Finally, we calculated the height deficit for each subject as the difference between midparental height and PAH. The height deficit of this cohort at baseline was 14.3 ± 7.7 cm and decreased to 7.9 ± 8.3 ($P = .02$) at the end of treatment, again indicating a positive effect of histrelin on growth.

D. *Effect on adult height*

We then examined the growth of the sub-group of the 10 individuals (8 females) who reached adult height (Table 2). Adult height in females was 153.8 ± 5 cm compared to their

Table 1. Subject characteristics ($n = 15$)

	Onset of therapy	End of therapy
Age (yrs)	7.7 ± 1.5	11 ± 1.65
Height z	1.15 ± 1.4	0.45 ± 1.17*
Weight z	1.5 ± 0.9	1.3 ± 0.7^{NS}
BMI z	1.45 ± 0.7	1.5 ± 0.5^{NS}
BA (yrs)	11.7 ± 1.4	13.5 ± 1.45*
BA/CA	1.57 ± 0.4	1.25 ± 0.25*
Predicted adult height (cm)	153.4 ± 7.3	160.5 ± 10.5**
Predicted adult height z	–2.33 ± 1.2	–1.35 ± 1.5**
Height deficit (cm)	14.3 ± 7.7	7.9 ± 8.3**
Height deficit z	2.1 ± 1	1.2 ± 1.2**
Midparental height z	–0.14 ± 0.63***	
Hydrocortisone (mg/m^2/day)	12.3 ± 3.2	13 ± 3^{NS}
17OHP (ng/dL)	2,367 ± 2,471 (161–7852)	3,563 ± 3,478^{NS} (188–13,198)
Androstendione (ng/dL)	119 ± 133 (19–528)	205 ± 239^{NS} (12–748)

Results are expressed as mean ± SD. *$P \leq .01$ between onset and end of therapy; **$P = .02$ between onset and end of therapy; ***$P = .002$ between midparental height z and height z at the end of therapy. NS = not significant.
Abbreviations: 17OH, 17 hydroxyprogesterone; BA, bone age; CA, chronological age; SD, standard deviation; yr, year.

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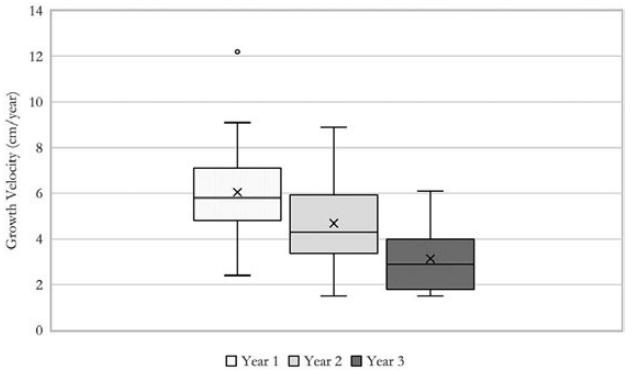

Figure 1. Annual growth velocity during histrelin therapy for patients with CAH. Box plots demonstrate the median, 25th and 75th percentiles, and full range. Outliers are noted by single data points above or below each plot. Data on the last 2 years are not included because of the small number of subjects.

Table 2. Subject characteristics for those who reached final height (n = 10; 8 females)

	Onset of therapy	End of therapy	Assessment at Adult Height
Age (yrs)	8 ± 1.4	11 ± 1.3	
Height z	1.34 ± 1.6	0.5 ± 1.4*	–1.42 ± 0.9
Weight z	1.7 ± 1	1.42 ± 0.8	0.99 ± 0.8 ¥
BMI z	1.6 ± 0.8	1.54 ± 0.6	1.43 + 0.6 ¥
BA (yrs)	11.5 ± 1.5	13.7 ± 1.6*	
BA/CA	1.5 ± 0.4	1.25 ± 0.3**	
Predicted Adult Height (cm)	152.85 ± 6.6	156.9 ± 6.8**	
Predicted Adult Height z	–1.96 ± 1.1	–1.38 ± 0.9**	
Height Deficit (cm)	12.6 ± 7	8.5 ± 6.8**	
Height deficit z	1.9 ± 1	1.3 ± 0.9**	
Midparental Height z	–0.06 ± 0.5***		
Hydrocortisone (mg/m^2/day)	12.5 ± 3.3	13.5 ± 2.8^{NS}	
17OHP (ng/dL)	2,403 ± 2,234 (161–7290)	4,238 ± 3,878 (524–13 198)	
Androstendione (ng/dL)	147 ± 153 (19–528)	283 ± 262 (51–748)	

Results are expressed as mean ± SD. *$P \leq .01$ between onset and end of therapy; **$P = .02$ between onset and end of therapy; ***$P = .01$ between midparental height z and final height z; ¥ = not significant among all 3 measurements. Abbreviations: 17OH, 17 hydroxyprogesterone; BA, bone age; CA, chronological age; yr, year.

midparental height of 163 ± 3.5 cm. Adult height in males was 161.6 ± 7.6 cm compared to their midparental height of 175 ± 0.63 cm. Height z scores decreased during the course of therapy from 1.34 ± 1.6 to 0.5 ± 1.4 ($P = .01$), indicating a decrease in height velocity. BA/CA also decreased (from 1.5 ± 0.4 to 1.25 ± 0.3, $P = .02$), while the PAH z scores improved (from –1.96 ± 1.1 to –1.38 ± 0.9, $P = 0.02$). Adult height z was –1.42 ± 0.9 (range –2.7 to –0.08), which was significantly lower than midparental height z ($P = .01$) and initial PAH z ($P < .01$). The difference between adult height z and miparental height z was –1.43 ± 0.95. Weight and BMI z at final height were 0.99 ± 0.82 and 1.43 ± 0.6, respectively. There was no difference in weight and BMI z scores during histrelin therapy and final anthropometric measurements.

E. *Classic versus nonclassic patients*

Our cohort included 4 patients with nonclassic disease (3 females, 1 male). All patients presented initially with premature adrenarche and were treated with hydrocortisone for

a minimum of 1 year prior to initiation of histrelin therapy. Growth data in classic versus nonclassic patients are summarized on Table 3. At baseline, there was a trend toward worse BA/CA, PAH z scores, and height deficit z scores in patients with classic disease compared to nonclassic. The lack of significance likely reflects the small sample size. BA/CA, PAH z scores, and height deficit z scores improved with histrelin administration in the classic group. In children with nonclassic disease, BA/CA improved with therapy. Changes in PAH and height deficit were slightly outside the range of statistical significance. The small sample size should be taken into account when interpreting these data.

F. *Additional therapy with an aromatase inhibitor*

Four boys received additional therapy with an aromatase inhibitor, and their data were compared to the rest of the subjects (Table 4). At baseline, there was a trend toward worse BA/CA, PAH z scores, and height deficit z scores in patients treated with an aromatase inhibitor compared to those who did not receive this therapy. The lack of significance likely reflects the small sample size. BA/CA and PAH z improved with histrelin therapy in both subgroups. Growth velocities (cm/year) were 6.7 ± 2.1, 4.8 ± 2.1, and 4.2 ± 2.3 in years 1 through 3 in the aromatase treated group (P = .30). In the nonaromatase group, growth velocities (cm/year) were 5.8 ± 2.6, 4.6 ± 2.2, and 2.3 ± 0.8 in years 1 through 3 (P = .01). None of the boys treated with an aromatase inhibitor has reached adult height.

3. Discussion

This retrospective review reports on the growth outcomes of histrelin therapy in children with CAH and early or precocious puberty at a single institution. We observed that pubertal suppression with histrelin implantion slowed down BA advancement, thus allowing participants to achieve some recovery of their height deficit and improvement in PAH. Subgroup analysis on individuals who completed their growth indicates that adult height remains compromised relative to population mean and midparental height.

Table 3. Subject characteristics grouped as having classic vs. nonclassic disease

	Classic CAH (n = 11)		Nonclassic CAH (n = 4)	
	Onset of therapy	**End of therapy**	**Onset of therapy**	**End of therapy**
Age (yrs)	7.4 ± 1.6	10.8 ± 1.9	8.9 ± 0.73	11.5 ± 0.4
Height z	1.2 ± 1.5	0.5 ± 1.3	0.97 ± 1.2	0.3 ± 0.75
Weight z	1.6 ± 0.9	1.4 ± 0.7	1.25 ± 1	1.09 ± 0.7
BMI z	1.6 ± 0.7	1.6 ± 0.6	1.09 ± 0.8	1.3 ± 0.5
BA (yrs)	11.96 ± 1.2	13.9 ± 1.4	11.4 ± 1.5	12.4 ± 1.1
BA/CA	1.68 ± 0.4	1.3 ± 0.3 *	1.28 ± 0.16	1.07 ± 0.07 *
PAH (cm)	152.1 ± 7.7	158.9 ± 11.4 *	157.1 ± 5	164.8 ± 8.1 NS
PAH z	–2.67 ± 1.2	–1.72 ± 1.3 *	–1.4 ± 0.86	–0.32 ± 0.5 NS
Height Deficit (cm)	16.7 ± 7.1	10.7 ± 6.7 *	8.2 ± 7.3	0.4 ± 8.5 NS
Height deficit z	2.46 ± 0.9	1.64 ± 0.95 *	1.16 ± 0.9	0.08 ± 1 NS
MPH (cm)	170.2 ± 7.9		164.8 ± 3.6	
Hydrocortisone (mg/m^2/day)	13.35 ± 2.9	14 ± 2.89	9.3 ± 1.5	10.6 ± 2.3
17OHP (ng/dL)	2,934 ± 2659 (200–7852)	4,445 ± 3682 (188–13 198)	810 ± 724 (161–1820)	1137 ± 736 (524–2157)
Androstendione (ng/dL)	144 ± 148 (19–528)	255 ± 264 (12–748)	52 ± 26 (23–79)	68 ± 23 (47–97)

Results are expressed as mean ± SD. *P ≤ .05 between onset and end of therapy within each group; NS = not significant.

Abbreviations: 17OH, 17 hydroxyprogesterone; BA, bone age; CA, chronological age; MPH, midparental height; PAH, predicted adult height; SD, standard abbreviation; yr, year.

Table 4. Subjects characteristics grouped according to treatment with an aromatase inhibitor

	Aromatase inhibitors (n = 4)		No aromatase inhibitors (n = 11)	
	Onset of therapy	End of therapy	Onset of therapy	End of therapy
Age (yrs)	6.5 ± 1.2	10.6 ± 2.7	8.3 ± 1.4	11.2 ± 1.2
Height z	0.83 ± 0.1	0.43 ± 0.8	1.26 ± 1.6	0.46 ± 1.4
Weight z	1.1 ± 0.4	1.2 ± 0.6	1.67 ± 1	1.4 ± 0.8
BMI z	1.1 ± 0.5	1.4 ± 0.3	1.6 ± 0.8	1.5 ± 0.6
BA (yrs)	12 ± 0.7	13 ± 1.2	11.7 ± 1.4	13.6 ± 1.6
BA/CA	1.89 ± 0.4	1.28 ± 0.3*	1.46 ± 0.4	1.24 ± 0.2*
PAH (cm)	153.1 ± 9.9	165.4 ± 14.8*	153.6 ± 6.7	158.6 ± 8.6*
PAH z	–3.28 ± 1.3	–1.6 ± 2*	–1.98 ± 1	–1.26 ± 0.9*
Height Deficit (cm)	22.1 ± 5.8	10.9 ± 11^{NS}	12 ± 6.9	7.2 ± 7.9*
Height deficit z	3 ± 0.78	1.5 ± 1.5^{NS}	1.9 ± 0.9	1.1 ± 1.1*
MPH (cm)	176 ± 7.2		166.2 ± 5.7	
Hydrocortisone (mg/m^2/day)	12.8 ± 2.5	13.6 ± 2.8	12.1 ± 3.4	12.9 ± 3.3
17OHP (ng/dL)	2761 ± 3477 (453–7852)	2471 ± 2519 (188–5165)	2224 ± 2200 (161–7290)	3960 ± 3792 (524–13 198)
Androstendione (ng/dL)	72 ± 67 (20–163)	53 ± 43 (12–101)	137 ± 149 (19–528)	261 ± 258 (47–748)

Results are expressed as mean ± SD. *$P \leq .05$ between onset and end of therapy within group; NS = not significant between onset and end of therapy within group.
Abbreviations: 17OH, 17 hydroxyprogesterone; BA, bone age; CA, chronological age; MPH, midparental height; PAH, predicted adult height; yr, year.

Although it is well recognized that children with CAH are at risk for precocious puberty (1–4), there is little evidence about the effect of GnRHa therapy on growth in this population (8–11). When combined with GH, depot leuprolide improves adult height compared to untreated historical controls (12, 13). In terms of the efficacy of leuprolide administered as a single agent, a single prospective study by Dacou-Voutetakis observed that 4 girls with CAH and precocity, who were treated with depot leuprolide (luteinizing hormone-releasing hormone), reached an adult height close to their midparental height. In contrast, their 4 untreated controls reached an adult height significantly lower than midparental (8). Two additional retrospective studies included 6 and 8 children, respectively, who received therapy with leuprolide for precocity. They reported a decrease in BA advancement and an improvement in adult predicted height (9, 10). Most recently, a larger retrospective study from China reported on 32 children with CAH and CPP; 11 children were treated with a GnRHa (depot triptorelin), 11 children received the combined therapy of GnRHa and letrozole, and 10 children received no intervention for their sexual precocity. The baseline characteristics of the three groups were the same. The near-final height z score of the GnRHa group was –1.8 ± 0.9 compared to –2.5 ± 1.0 in the untreated group. These values did not reach statistical significance (P = .06), a result that may be related to the small sample size. Children who received the combined GnRHa and letrozole therapy reached a taller near-final height (z = –1.3 + 0.8) compared to untreated (z = –2.5 ± 1.0, $P < .05$) (11). Additional studies are needed to confirm whether aromatase inhibitors alone or in combination with a GnRHa improve growth in children with CAH and sexual precocity. In our study, aromatase inhibitors were also used in combination with a GnRHa in 4 subjects; ultimately these subjects demonstrated similar growth outcomes to those who received only GnRHa. Our small sample size precludes us from reaching any conclusions about the use of these medications to improve growth in CAH.

Our study is the first to report on the efficacy of histrelin implantion in CAH. We observed an improvement in PAH despite a gradual decrease in annual growth velocity. Steroid treatment is unlikely to have contributed to the decreased growth rate, since the doses of hydrocortisone did not change significantly over the course of the study. A similar decrease in growth velocity has also been reported during the first 3 years of histrelin therapy in

non-CAH children with sexual precocity (19). In CAH, Soliman et al observed a decrease in growth rate and an improvement in PAH during pubertal suppression with leuprolide acetate (9). Another study of leuprolide acetate in 12 children with CAH found that an advanced BA at initiation of treatment was associated with diminished growth velocity (10). We explored similar correlations in our cohort and could not replicate these findings.

Multiple studies in CAH document a short adult height and a height deficit compared to midparental height. A recent meta-analysis, which included 35 studies of patients with classic CAH, reported an adult height z score of –1.38 (mean –1.56 to –1.20) and a difference from midparental height z score of –1.03 (–1.2 to –0.86) (11). In our cohort, adult height was improved compared to the pretreatment PAH, suggesting a beneficial effect of histrelin on growth. Despite therapy, however, the mean adult height in this study did not fare better than what is reported in the literature (11). Furthermore, the subjects had a poor height prognosis at the initiation of treatment. This finding may reflect the fact that many of our patients were in poor adrenal control, which is likely to lead to both sexual precocity and an advancement in BA. Therefore, the results of this study need to be interpreted while taking these factors into account.

GnRHa studies in CPP usually express growth outcomes of the therapy as the difference between PAH at initiation of treatment and achieved adult height (6). The results are variable and in the range of 2.7 to 6.97 cm (6). Randomized controlled studies have not been conducted. Similarly, our study does not have a control group. Furthermore, in this study, we assessed changes in growth by using height predictions, which are often imprecise. In this paper, we calculated PAH using the Bayley Pinneau method, which is frequently used in pediatric growth studies. This method was developed for healthy children and may not be applicable when therapies such as GnRHa are used. Indeed, a small body of literature suggests that the Bayley Pinneau method overestimates adult height in children with CPP who also experience BA advancement (6, 20, 21). Similar findings were reported more recently in a study in girls with onset of CPP between 6 and 8 years. The study included a group who was treated with GnRHa and a second group of untreated subjects (22). Both groups reached an adult height lower than their initial PAH (8 cm difference in the treated group vs 2.3 cm in the untreated group) (22). With respect to CAH, a study of height predictions by Bayley Pinneau in children with CAH who did not received GnRHa therapy found that predictions, again, overestimate adult height (23). The true benefit of histrelin on growth in CAH remains, therefore, uncertain. Prospective controlled studies are clearly needed to determine the growth benefits of such therapy.

There are a number of limitations associated with this work. Beyond the limitation of the retrospective study design, the number of subjects is small, which did not allow us to explore factors that may influence response to treatment, including gender, age on presentation, BA advancement or degree of adrenal androgen suppression. GnRHa administration improves adult height in girls with precocity treated before the age of 6 years, while no such benefits are seen when the therapy is instituted after the age of 8 years (6). Whether the same is true in CAH has to be further examined. Finally, our cohort included 4 children who also received treatment with an aromatase inhibitor, which may have favorably influenced growth results. Nonetheless, our data remain important given the paucity of information on the effects of pubertal suppression on growth and adult height in CAH. Potential differences between various GnRHa, such as depot leuprolide and histrelin implant, on growth in CAH need to be further determined.

In summary, this retrospective cohort study suggests that pubertal suppression with histrelin implantation improves growth in children with CAH and precocious or early puberty, albeit final height remains lower than population means and midparental height. Additional prospective controlled studies are warranted to validate these findings, as short stature occurs frequently in these individuals and pubertal suppression with GnRHa is commonly prescribed. Possible differences in growth outcomes among various GnRHa also need to be also determined.

Additional Information

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Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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