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Effect of Antiandrogen, Aromatase Inhibitor, and Gonadotropin-releasing Hormone Analog on Adult Height in Familial Male Precocious Puberty

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Abstract

Objective—Antiandrogen, aromatase inhibitor, and gonadotropin-releasing hormone analog (GnRHa) treatment normalizes growth rate and bone maturation and increases predicted adult height (AH) in boys with familial male-limited precocious puberty (FMPP). To evaluate the effect of long-term antiandrogen, aromatase inhibitor, and GnRHa on AH, boys with FMPP who were treated were followed to AH.

Study Design—Twenty-eight boys with FMPP, referred to the National Institutes of Health, were started on antiandrogen and aromatase inhibitor at 4.9 ± 1.5 years of age; GnRHa was added at 6.9 ± 1.5 years of age. Treatment was discontinued at 12.2 ± 0.5 years of age (bone age, 14.4 ± 1.3). AH was assessed at 16.4 ± 1.3 years of age (bone age, 18.5 ± 0.6).

Results—AH (mean ± standard deviation) for all treated subjects was 173.6 ± 6.8 cm (−0.4 ± 1.0 standard deviation relative to adult US males). For 25 subjects with pretreatment predicted AH, AH significantly exceeded predicted AH at treatment onset (173.8 ± 6.9 vs 164.9 ± 10.7 cm; $P < .001$), but fell short of predicted AH at treatment discontinuation (177.3 ± 9.0 cm; $P < .001$). For 11 subjects with maternal or sporadic inheritance, the mean AH was 3.1 cm (0.4 standard deviation score) below sex-adjusted midparental height (175.4 ± 5.8 vs 178.5 ± 3.1 cm [midparental height]; $P = .10$). For 16 subjects with affected and untreated fathers, AH was significantly greater than fathers' AH (172.8 ± 7.4 vs 168.8 ± 7.2 cm; $P < .05$).

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The authors declare no conflicts of interest.

Conclusions—Long-term treatment with antiandrogen, aromatase inhibitor, and GnRHa in boys with FMPP results in AH modestly below sex-adjusted midparental height and within the range for adult males in the general population.

Familial male-limited precocious puberty (FMPP, also termed testotoxicosis) results from a luteinizing hormone (LH) receptor gene activating mutation.[1–7] The mutation can occur de novo, but is usually inherited as an autosomal dominant. Affected males experience early pubertal development, usually by 3 years of age, with accelerated growth and bone maturation, premature epiphyseal fusion, and short adult stature.

Two therapeutic approaches, involving antiandrogens, aromatase inhibitors, and gonadotropin-releasing hormone analog (GnRHa; after the onset of central puberty), or steroid biosynthesis inhibitors, have resulted in reduced rate of linear growth rate, bone maturation, and virilization in boys with FMPP.[8–15] Only limited data, however, are available on the adult height (AH) of patients after long-term treatment. For 5 boys treated for a median of 6.2 years with the steroidogenesis inhibitor ketoconazole, mean ± standard deviation (SD) AH (and height SD score [SDS]) were 173 ± 14 cm (−0.3 ± 1.4 SDS), which was significantly greater than the pretreatment predicted AH of 165 ± 12 cm and similar to the midparental height (MPH) of 175 ± 9 cm.[16] By contrast, mean ± SD near-AH SDS for 7 boys with FMPP treated with cyproterone acetate (n = 4) or ketoconazole (n = 3), combined with GnRHa (after central puberty onset) in 4 boys and with medroxyprogesterone acetate or anastrozole in 1 subject each, was considerably less, at −1.5 ± 1.0 SDS.[17]

Since the mid-1980s, we have investigated whether antiandrogen (spironolactone) and aromatase inhibitor (testolactone or anastrozole), combined with GnRHa (daily deslorelin or depot leuprolide) after central puberty onset, can normalize growth, pubertal development, and AH in boys with FMPP.[11] Previous interim reports have described the effects of this treatment regimen on linear growth, bone maturation, and predicted AH.[10,11] The current report describes the AH outcome in 28 boys with FMPP who received long-term treatment with this regimen and were then followed until attainment of AH.

Methods

The Institutional Review Board of the National Institute of Child Health and Human Development approved the protocol, “Spironolactone and Testolactone Treatment of Boys with Familial Isosexual Preocious Puberty (National Institutes of Health 85-CH-0016; NCT00001202),” in 1985, and enrollment of subjects occurred between 1985 and 2001. Written informed consent was obtained from parents, and assent was obtained from children when appropriate. The study was in full compliance with the Health Insurance Portability and Accountability of 1996.

Subjects were assessed at the National Institutes of Health Clinical Center every 6 months while on study medications until the initiation of GnRHa, then yearly until AH was reached. At each visit, pubertal staging, routine laboratory measures (including complete blood count, electrolytes, blood urea nitrogen, creatinine, blood glucose, hepatic panel, mineral panel, total cholesterol, and thyroid function studies), reproductive hormone levels (including testosterone, and baseline and GnRH-stimulated LH and follicle-stimulating hormone [FSH]

levels) were obtained as described.[9–11] Also at each visit, the average of ≥3 stadiometer heights was recorded, and bone age (BA) films were interpreted by several radiologists from the National Institutes of Health (all with expertise in the interpretation of BA films), without knowledge of treatment status, using the method of Greulich and Pyle.[18] The predicted AH was determined by the Bayley-Pinneau method.[19] AH measurement was obtained when BA was ≥17 years of age (or up to 2 years later when additional follow-up visits were available).

Parental and fraternal AHs were measured at the Clinical Center when possible, and reported AHs were used for family members not available for measurement. Sex-adjusted MPH for subjects with unaffected fathers (n = 11) was calculated as follows:

$$\frac{(paternal\ height\ [cm] + maternal\ height\ [cm] + 13\ cm)}{2}$$

Corrected, sex-adjusted MPH for subjects with untreated affected fathers (n = 16) was calculated as follows, to correct for the 7.3-cm mean height decrement of affected fathers relative to US adult males[20]:

$$\frac{\begin{array}{c}(\text{paternal height } [cm] + 176.1\ cm\ [\text{mean normal US adult male height at age } 19] \\ -168.8\ cm\ [\text{mean paternal height of affected fathers}] + \text{maternal height } [cm] + 13\ cm)\end{array}}{2}$$

Spironolactone was administered daily, every 12 hours, in 2 equally divided oral doses. The dose was increased weekly from 1.5 to 3.0 mg/kg per day and then 5.7 mg/kg per day. Because spironolactone can deplete sodium and retain potassium, liberal intake of salt and moderate intake of high-potassium foods were recommended. In addition, subjects and parents were instructed to withhold spironolactone during diarrhea, vomiting, or other illness involving increased fluid loss or decreased fluid intake. For all 28 subjects, mean ± SD treatment duration was 6.9 ± 1.8 years (range, 2.7–10.3) for spironolactone.

Testolactone was administered daily in 4 equally divided oral doses (every 6 hours) from 1985 to 1994 and then, to enhance convenience, in 3 equally divided oral doses (every 8 hours). Testolactone therapy was increased weekly from 20 to 30 mg/kg per day and then 40 mg/kg per day. When testolactone became unavailable in 2005, the 5 subjects remaining on study drug transitioned to anastrozole, 1 mg daily (oral) at bedtime. For all 28 subjects, mean ± SD treatment duration was 6.9 ± 1.8 years (range, 2.7–10.3) for testolactone and 0.3 ± 0.8 years (range, 0.0–3.0) for anastrozole.

The decision to start GnRHa was based on both clinical evidence of central puberty (an acute increase in the signs and symptoms of puberty) and a GnRH stimulation test that was either frankly pubertal (peak LH > 20 mIU/mL and/or peak LH greater than peak FSH) or approaching a pubertal response, as described.[9–11] Initially, all subjects in secondary central puberty were treated with deslorelin 4 g/kg per day subcutaneously each evening. When deslorelin became unavailable in 2003, 4 subjects who were still on the study drug were transitioned to 1-month depot leuprolide, 7.5–15 mg (based on weight and response) every 3

weeks. Also, 3 subjects who had not yet been treated with GnRHa were later treated with depot leuprolide. Once GnRHa was initiated, GnRH stimulation testing was performed every 12 months to ensure suppression of secondary central puberty (suppressed basal and peak LH and FSH levels). For the 27 AH subjects treated with GnRHa, the mean ± SD treatment duration was 5.5 ± 1.6 years (range, 2.1–8.3) for deslorelin and 2.8 ± 0.9 years (range, 1.5–4.3) for leuprolide.

All weight-based medication dosages were adjusted at 6-month intervals.

Statistical Analyses

Among the 39 total study subjects, 8 patients who dropped out of the study before attaining AH were excluded from this completer analysis. Study discontinuation resulted from parent decision owing to divorce (n = 2), desire to receive care closer to home (n = 1), and inconvenience of study visits (n = 5). No subjects discontinued owing to adverse effects or perceived lack of efficacy. Three additional subjects were excluded because they had not yet attained AH, leaving 28 subjects with measured AHs as the subject of this report.

All data were expressed as mean ± SD. AH measurements were compared with predicted AH at start of treatment, predicted AH at end of treatment, sex-adjusted MPH, paternal height, and fraternal height using the 2-tailed paired Student *t* test. AH comparison between paternally versus maternally inherited (or sporadic) cases was made with the 2-tailed Student *t* test.

Results

All 28 subjects had a documented heterozygous activating mutation of the LH receptor (23 Asp578Gly, 2 Asp564Gly, 1 Asp572Val, 1 Ile575Leu, 1 Met398Thr; Tables I and II). Sixteen inherited the mutation from their affected, untreated father, nine from their mother, two had de novo mutations, and one had a mutation of unknown source (mother did not have the mutation; father unavailable for analysis). There was no known consanguinity between study subjects, although approximately one-half of the subjects with the most common mutation (Asp578Gly) reported having ancestors from Dothan, Alabama, suggesting that some of may have been distant relatives. Mean chronological age and BA at start of therapy were 4.9 ± 1.5 and 9.7 ± 3.5 years of age, respectively (mean BA advancement 4.8 ± 2.6 years). GnRHa was started at a mean chronological age of 6.9 ± 1.5 years (mean BA, 12.1 ± 1.6).

AH was significantly greater than pretreatment predicted AH (173.8 ± 6.9 cm [−0.3 ± 0.9 SDS] vs 164.9 ± 10.7 cm [−1.5 ± 1.5 SDS]; n = 25; $P < .001$; Figure). Three subjects could not be included in this analysis because their pretreatment BAs were too immature for a Bayley-Pinneau height prediction. Analysis of subjects by parental inheritance showed similar, statistically significant increases in AH compared with pretreatment predicted AH for individuals with affected fathers (172.4 ± 7.8 cm vs 163.7 ± 10.7 cm; n = 14; $P < .001$; Figure) and for those with maternal or sporadic inheritance (176.5 ± 4.8 cm vs 166.5 ± 11.7 cm; n = 10; $P < .05$; Figure). One subject with unknown inheritance could not be analyzed according to parental origin.

AH decreased significantly below the estimated predicted AH at treatment discontinuation (173.6 ± 6.8 cm [−0.4 ± 0.9 SDS] vs 177.2 ± 9.0 cm [0.1 ± 1.2 SDS]; $n = 28$; $P < .001$; Figure). Analysis of subjects by parental inheritance demonstrated similar, statistically significant shortfalls in AH versus end-of-treatment predicted AH for individuals with affected fathers (172.8 ± 7.4 cm vs 176.8 ± 9.9 cm; n = 16; $P < .001$; Figure) and for those with maternal or sporadic inheritance (175.4 ± 5.8 cm vs 178.5 ± 7.9 cm; n = 11; $P < .05$; Figure).

In 11 subjects with either maternal inheritance or sporadic FMPP, whose fathers were unaffected by FMPP and for whom sex-adjusted MPH provided a meaningful estimate of genetic height potential, AH did not differ significantly from MPH (175.4 ± 5.8 cm [−0.1 ± 0.8 SDS] vs 178.5 ± 3.1 cm [0.3 ± 0.4 SDS], respectively; $P = .10$; Figure). Of note, AH for unaffected fathers was 181.0 ± 0.3 cm (range, 175.3–185.4), which is 4.9 cm greater than the mean normal US adult male height at age 19 years.[20]

In the 16 boys with affected fathers, a similar comparison between AH and paternally corrected MPH (calculated after correcting paternal heights for the mean 7.3-cm deficit in affected father height versus mean National Health Examination Survey male height data[21]) did reach statistical significance (172.8 ± 7.4 cm [AH] vs 175.9 ± 6.3 cm; $P < .05$; Figure), although the mean decrease in AH versus MPH (sex-adjusted and/or paternally corrected) was identical (3.1 cm [0.4 SDS]).

Analysis of all 27 subjects with known inheritance (paternal, maternal, or sporadic) similarly demonstrated a significant shortfall between AH and sex-adjusted, paternally corrected MPH (173.8 ± 6.8 cm [AH] vs 177.0 ± 5.3 cm; n = 27; $P < .01$; Figure).

AH was greater than paternal height for the 16 subjects with FMPP-affected, untreated fathers (172.8 ± 7.4 cm vs 168.8 ± 7.2 cm; $P < .05$; Figure). Similarly, the mean AH was greater than fraternal height for the 2 subjects with affected, untreated brothers (168.6 cm vs 157.5 cm [−1.1 vs −2.6 SDS] and 185.9 cm vs 170.2 cm [1.3 vs −0.9 SDS]).

The AH in subjects with paternal inheritance did not differ significantly from AH in those with maternal or sporadic inheritance (172.8 ± 7.4 cm [−0.5 ± 1.0 SDS] vs 175.4 ± 5.8 cm [−0.1 ± 0.8 SDS]; $P < .4$).

The first-generation aromatase inhibitor testolactone was changed, late in the study, to anastrozole, and daily deslorelin was changed to depot leuprolide. There was no acute effect of these changes on growth rate or bone maturation (data not shown). The transition from deslorelin to depot leuprolide did not affect the baseline and GnRH-stimulated LH and FSH levels. The shift from testolactone to anastrozole did not alter serum testosterone levels (data not shown). Serum estradiol levels were not assessed because testolactone (and/or its metabolites) cross-reacted in the available estradiol assay.

Subjects were highly compliant with medication and evaluation regimens as assessed by visit history, return of unused study medication, parental and caregiver report, and pubertal suppression as measured by height velocity, rate of bone maturation, and baseline and stimulated LH and FSH levels during GnRH-stimulation testing (once GnRHa was initiated

for secondary central puberty). Subjects and families were highly motivated to comply with treatment and follow-up regimens because the androgen blockade achieved while on the study drug resulted in significant and immediate improvement in the signs and symptoms of precocious puberty.

No deaths or treatment-related severe adverse events occurred during the study. No hepatic, renal, hematologic, or lipid abnormalities were attributed to study medications. Transient, mild abdominal pain, nausea, and/or vomiting occurred occasionally after starting testolactone treatment, and resolved quickly in all cases without dose reduction. One episode of hyponatremia (sodium 125 mEq/L [125 mmol/L]) was observed during poor fluid intake, fever, and pneumonia in a subject in whom spironolactone had been continued despite the protocol provision and instructions to discontinue spironolactone during acute illness involving fluid loss or reduced intake. The hyponatremia resolved spontaneously after temporarily discontinuing spironolactone. The potassium level remained normal.

Discussion

The current study of 28 boys with FMPP, treated from early childhood with a combination of antiandrogen, aromatase inhibitor, and GnRHa (after premature secondary gonadotropin activation), represents the largest study to date of AH after long-term antiandrogen and aromatase inhibitor treatment in FMPP. Mean achieved AH was only modestly (−0.4 SD units) below that of the general US male population, or the child's own MPH (−0.4 SD units), and for boys with affected, untreated fathers, it was significantly greater than the mean AH of their fathers, which was −1.0 SDS (16th percentile) relative to US adult males. Bayley-Pinneau predicted AH increased throughout treatment, but height prediction after mean treatment duration of 7.3 years significantly overestimated actual AH (mean overprediction, 0.5 SD units). This overestimation of AH at treatment end, which has been observed in other precocious puberty studies,[20,22] may be attributable to the underlying disease process or prediction method inaccuracies, and has implications for physician, patient, and parental expectation. Despite the regimen's complexity, treatment was well-tolerated with only minor adverse events.

Several factors may explain the 0.4 SD-unit AH decrement compared with mean US male AH and sex-adjusted MPH. First, mean BA was advanced 4.8 years at treatment onset, and whether delayed treatment can normalize AH completely at this point in development is unclear. Second, because estrogen levels of normal boys are undetectable in all but the most sensitive research assays, it was not possible to confirm whether testolactone or anastrozole reduced estrogen levels continuously to the normal childhood range. Third, compliance with study medication administration was not assessed quantitatively, and nonadherence to study medication must be considered a potential factor in any long-term study involving children.

Compared with previous reports, the current AH data are consistent with those of Sorianoo-Guillén et al,[16] who observed a mean AH SDS of −0.3 in 5 boys with FMPP after long-term treatment with ketoconazole. By contrast, the current AH values seem to be greater than the mean near-final height SDS of −1.5 observed by Almeida et al[17] in 7 boys treated with

ketoconazole or cyproterone acetate. Because of multiple study design differences, the reasons for this apparent difference are unclear.

During the 3 decades over which the current study was conducted, aromatase inhibitors improved in potency and convenience, depot versus daily GnRHa became established in pediatric patients, and study drugs were changed when 2 of the 3 original study drugs became unavailable. The study design does not allow determination of possible differences in effectiveness between initial and subsequent choices of aromatase inhibitor or GnRHa. In addition, the study did not permit comparison of spironolactone with bicalutamide, a more potent androgen receptor blocker. Thus, the results should be viewed as a proof of concept for combined antiandrogen and aromatase inhibitor treatment to normalize growth rate, bone maturation, and pubertal progression and, when combined with GnRHa after central puberty onset, to achieve a near-normal AH outcome in boys with FMPP. Further long-term studies, such as those that are ongoing,[12–15] will be required to determine whether newer, more convenient antiandrogen and aromatase inhibitor combinations can achieve similar or better results, and to provide more evidence on the benefits and risks of antiandrogen and aromatase inhibitor versus ketoconazole-induced blockade of steroidogenesis. We recommend that physicians support such ongoing studies so that information in this rare disorder can be accrued more rapidly.

Initially, only an antiandrogen and an aromatase inhibitor were administered to boys with FMPP, with the goal of blocking androgen effects on masculinization and behavior, and estrogen effects on growth rate and bone maturation.[9] We added GnRHa to our treatment regimen because of unequivocal height velocity and/or BA acceleration coincident with pubertal gonadotropin secretion and testicular enlargement.[10] However, the need for GnRH treatment may be specific to the early generation aromatase inhibitor and antiandrogen that were used during the majority of this study. With more potent aromatase inhibitors and antiandrogens now available, it may be possible to block the effects of central puberty with the combined aromatase inhibitor and antiandrogen regimen alone, in which case the cost and burden of GnRHa treatment may be avoidable. Because all but one subject received all 3 components of this regimen, the relative contributions of the different components, and in particular of GnRHa after central puberty had begun, are unknown.

Bone mineral density was not included as an outcome measure when this study was designed because methods of bone density measurement were still evolving, normative data for children were not available, and estrogen's role in male bone density was less well-appreciated before the discovery of men with osteoporosis owing to estrogen receptor or aromatase deficiency.[23,24] Although this lack of bone density data represents a knowledge gap for the current treatment, the age at onset and duration of estrogen suppression in our subjects was similar to that of boys with central precocious puberty treated with GnRHa—a setting in which bone density after treatment has been shown to be normal.[25]

The discovery that estrogen mediates epiphyseal fusion has prompted interest in aromatase inhibitor treatment as a potential means to increase AH in other pediatric conditions associated with short stature, such as constitutional delay of growth and adolescence,[26] growth hormone deficiency,[27] and idiopathic short stature.[28–32] Although the improved AH

outcome in the current study of boys with FMPP is consistent with this potential, we agree with the recommendation to complete ongoing long-term clinical trials before expanding pediatric aromatase inhibitor treatment to a much wider patient group.[33,34]

In conclusion, the combined regimen of an antiandrogen, an aromatase inhibitor, and GnRHa substantially achieved the study goals of normalizing growth, development, and AH in boys with FMPP. The regimen, although complex, was well-tolerated with only minor adverse events. Until more specific therapy is developed for this rare disorder, we recommend antiandrogen and aromatase inhibitor treatment, with added GnRHa where clinically appropriate, as a safe and effective approach based on results observed over the past 30 years.

Data Analysis

Data were analyzed by Ellen W. Leschek. ■

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Abbreviations

AH	Adult height
BA	Bone age
FMPP	Familial male-limited precocious puberty
FSH	Follicle-stimulating hormone
GnRHa	Gonadotropin-releasing hormone analog
LH	Luteinizing hormone
MPF	Midparental height
SD	Standard deviation
SDS	SD score

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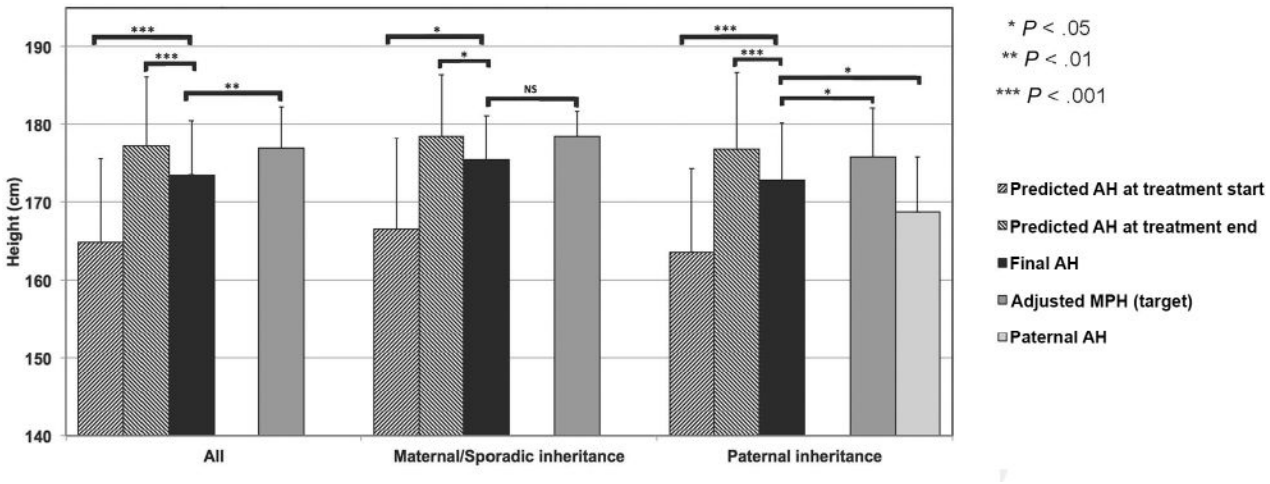

Figure.

Predicted AH at treatment start and end, final AH, and adjusted midparental (target) height in all treated FMPP patients (left-hand bars, n = 28). Center and right-hand bars indicate results for patients with maternal or sporadic inheritance (center bars, n = 11) and those with paternal inheritance (right-hand bars, n = 16). Data for boys with paternal inheritance include a bar (far right) indicating paternal AH for their affected untreated fathers. One patient had unknown inheritance. Values are expressed as mean ± SD.

Table I

Patient characteristics at baseline, treatment initiation, treatment discontinuation, and AH

Characteristics	All Subjects (N = 28)	Paternal Inheritance (n = 16)	Maternal (n = 9) or Sporadic (N = 2) Inheritance	Unknown Inheritance (n = 1)
Initiation of antiandrogen/aromatase inhibitor (baseline)				
CA (y)	4.9 ± 1.5	4.9 ± 1.5	4.8 ± 1.7	6.2
BA (y)	9.7 ± 3.5	9.7 ± 3.4	9.3 ± 3.8	12.5
BA minus CA (y)	4.8 ± 2.6	4.8 ± 2.6	4.6 ± 2.7	6.3
Predicted AH (cm)	164.9 ± 10.7§	163.7 ± 10.7§	166.5 ± 11.7§	165.8
Predicted AH (SDS)	−1.7 ± 1.5§	−1.8 ± 1.5§	−1.4 ± 1.6§	−1.5
MPH (cm)*	177.0 ± 5.3¶	175.9 ± 6.3	178.5 ± 3.1	N/A
MPH (SDS)*	0.0 ± 0.7¶	−0.1 ± 0.9	0.2 ± 0.4	N/A
Initiation of GnRHa**				
CA (y)	6.9 ± 1.5	7.0 ± 1.5	6.9 ± 1.6	6.6
BA (y)	12.1 ± 1.6	12.2 ± 1.6	11.9 ± 1.7	13.5
BA minus CA (y)	5.2 ± 1.9	5.3 ± 1.6	5.0 ± 2.2	6.9
Discontinuation of treatment				
CA (y)	12.2 ± 0.5	12.2 ± 0.6	12.2 ± 0.6	12.1
BA (y)	14.4 ± 1.3	14.7 ± 1.5	14.0 ± 0.9	14.5
BA minus CA (y)	2.2 ± 1.5	2.4 ± 1.7	1.8 ± 1.2	2.5
Antiandrogen/aromatase inhibitor treatment duration (y)	7.3 ± 1.8	7.3 ± 1.7	7.5 ± 2.1	5.9
GnRHa treatment duration (y)	5.3 ± 1.6	5.3 ± 1.4	5.3 ± 2.0	5.5
Predicted AH (cm)	177.2 ± 9.0	176.8 ± 9.9	178.5 ± 7.9	170.1
Predicted AH (SDS)	0.1 ± 1.3	0.0 ± 1.4	0.2 ± 1.1	−1.0
AH (study end)				
CA (y)	16.4 ± 1.3	16.6 ± 1.5	16.1 ± 0.9	15.1
BA (y)	18.5 ± 0.6	18.5 ± 0.4	18.5 ± 0.7	19.0
AH (cm)	173.6 ± 6.8	172.8 ± 7.4	175.4 ± 5.8	166.8
AH (SDS)	−0.4 ± 1.0	−0.5 ± 1.0	−0.1 ± 0.8	−1.4

CA, Chronological age.

*MPH calculation depends on mode of inheritance:

Subjects with maternal or sporadic inheritance: MPH = (father's height [cm] + mother's height [cm] + 13 cm)/2

Subjects with paternal inheritance: MPH = (father's height [cm] + [176.1 cm† − 168.8 cm‡] + mother's height [cm] + 13 cm)/2

†Mean adult male height according to the 2000 National Health Examination Survey.[21]

‡Mean paternal height (affected fathers).

§Three subjects started treatment at BA too low to determine predicted height (inheritance—2 paternal, 1 maternal).

¶One subject with unknown inheritance could not be included in these calculations.

**One subject (with paternal inheritance) declined treatment with GnRHa.

Table II

Patient characteristics during interval between previously reported analysis (Leschek et al[11]) and AH measurement of patients in current analysis

CAs* (y)	Patient No.	Height Velocity (cm/y)	BA (y)	Testicular Volume (mL)	Peak LH† (IU/L)	Peak FSH† (IU/L)	Testosterone (ng/dL)
6	6	6.4 ± 2.0	11.0 ± 2.0	6.5 ± 1.4	4.8 ± 3.3	2.8 ± 2.5	209 ± 100
7	9	6.3 ± 1.8	11.4 ± 1.3	7.1 ± 1.2	6.6 ± 4.3	3.5 ± 2.7	195 ± 138
8	8	6.6 ± 1.4	11.7 ± 0.9	7.9 ± 0.9	7.2 ± 10.2	1.8 ± 1.7	204 ± 113
9	9	5.4 ± 1.3	12.0 ± 1.1	8.3 ± 1.4	1.7 ± 2.1	1.4 ± 1.8	210 ± 141
10	10	5.6 ± 1.8	12.7 ± 0.9	8.5 ± 1.6	2.1 ± 1.0	1.9 ± 1.3	214 ± 170
11	12	4.6 ± 1.3	13.2 ± 0.6	8.5 ± 2.3	2.7 ± 2.0	2.1 ± 1.9	235 ± 167
12	12	4.7 ± 2.3	13.8 ± 0.6	10.7 ± 5.7	3.0 ± 3.3	1.8 ± 1.8	232 ± 221
13	14	6.3 ± 6.0	15.3 ± 1.2	14.9 ± 5.2	No data	No data	414 ± 162
14	17	3.7 ± 2.8	16.6 ± 0.9	16.7 ± 4.6	18.5 ± 7.0	11.7 ± 7.3	443 ± 186
15	16	2.1 ± 1.7	17.3 ± 0.9	17.0 ± 4.3	25.3 ± 17.5	11.2 ± 7.4	507 ± 217
16	13	0.8 ± 0.6	18.2 ± 0.6	17.2 ± 2.9	24.9 ± 22.0	12.3 ± 11.1	499 ± 234
17	5	0.6 ± 0.7	18.8 ± 0.3	16.5 ± 5.2	No data	No data	432 ± 238

CA, Chronologic age.

Data are mean ± SD of all study measurements during interval between previously reported and current analysis.

*Chronological age (y) of patient at previously reported analysis (Leschek et al[11]).

†GnRH stimulation testing was not performed when GnRHa was unavailable owing to discontinuation by the manufacturer.