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

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**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 ± SD) for all treated subjects was 173.6 ± 6.8 cm (–0.4 ± 1.0 SD 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 SD 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; $P < .05$).

**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. *(J Pediatr 2017;190:229-35).*

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 ± SD AH (and height 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.

| | |
|---|---|
| AH | Adult height |
| BA | Bone age |
| FMPP | Familial male-limited precocious puberty |
| FSH | Follicle-stimulating hormone |
| GnRHa | Gonadotropin-releasing hormone analog |
| LH | Luteinizing hormone |
| MPH | Midparental height |

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## 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 Act 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 (**Tables I**).[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]:

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

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 cause sodium depletion and potassium retention, 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

**Table I. 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 |

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.