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**Review**

# Management of Growth Disorders in Puberty: GH, GnRHa, and Aromatase Inhibitors: A Clinical Review

**Nelly Mauras,[1] Judith Ross,[2] and Veronica Mericq[3]**

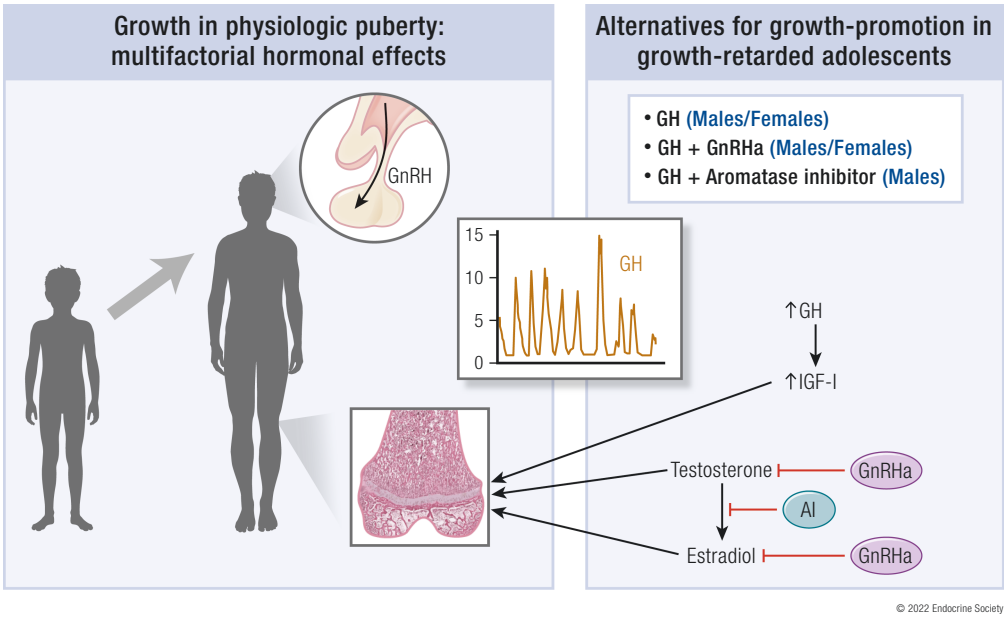
[1]Nemours Children's Health Jacksonville, FL 32207, USA
[2]Nemours Children's Health Wilmington, DE 19803, USA
[3]University of Chile, Santiago, Chile

**Correspondence:** Nelly Mauras, MD, Division of Endocrinology, Diabetes & Metabolism, Nemours Children's Health, 807 Children's Way, Jacksonville, FL 32207, USA. Email: nmauras@nemours.org

## Abstract

Pubertal children with significant growth retardation represent a considerable therapeutic challenge. In growth hormone (GH) deficiency, and in those without identifiable pathologies (idiopathic short stature), the impact of using GH is significantly hindered by the relentless tempo of bone age acceleration caused by sex steroids, limiting time available for growth. Estrogen principally modulates epiphyseal fusion in females and males. GH production rates and growth velocity more than double during puberty, and high-dose GH use has shown dose-dependent increases in linear growth, but also can raise insulin-like growth factor I concentrations supraphysiologically, and increase treatment costs. Gonadotropin-releasing hormone analogs (GnRHas) suppress physiologic puberty, and when used in combination with GH can meaningfully increase height potential in males and females while rendering adolescents temporarily hypogonadal at a critical time in development. Aromatase inhibitors (AIs) block androgen to estrogen conversion, slowing down growth plate fusion, while allowing normal virilization in males and stimulating longitudinal bone growth via androgen receptor effects on the growth plate. Here, we review the physiology of pubertal growth, estrogen and androgen action on the epiphyses, and the therapeutic impact of GH, alone and in combination with GnRHa and with AIs. The pharmacology of potent oral AIs, and pivotal work on their efficacy and safety in children is also reviewed. Time-limited use of AIs is a viable alternative to promote growth in pubertal males, particularly combined with GH. Use of targeted growth-promoting therapies in adolescence must consider the impact of sex steroids on growth plate fusion, and treatment should be individualized.

## Graphical Abstract






**Key Words:** short stature, puberty, GH, GnRHa, aromatase inhibitor, epiphyses

**Abbreviations:** AI, aromatase inhibitor; DEXA, dual-emission X-ray absorptiometry; ER, estrogen receptor; GH, growth hormone; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone analog; IGF, insulin-like growth factor; ISS, idiopathic short stature; KO, knockout; QoL, quality of life.

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## Physiology of Growth in Puberty

In normal physiology, the onset of puberty is driven by increased activity of the gonadotropin-releasing hormone (GnRH) pulse generator ("gonadostat") and a complex interplay of hypothalamic peptides, including GnRH, and kisspeptin and its cognate receptor GPR54 (1, 2). Puberty initiation is also the result of decreased tone of makorin, a suppressor of the gonadostat; makorin gene mutations cause precocious puberty (3). Gonadostat activation in turn increases luteinizing hormone/follicle-stimulating hormone pulsatility, beginning with higher amplitude night-time pulses, resulting in increased gonadal steroids. This results in the first pubertal changes, breast buds in girls and testicular enlargement in boys. Increase in gonadal steroids in turn results in marked increase in growth hormone (GH) production from the somatotropes. GH binds and activates the GH receptor, and a complex cascade of events, including intracellular phosphorylation of Jak/STAT kinases, results in the generation of insulin-like growth factor (IGF)-I. Downstream interactions by novel peptides further affect linear growth. Pregnancy-associated plasma protein A2, cleaves IGF-I from its binding proteins and effects free IGF-I bioavailability to the GH-sensitive tissues, including bone (4, 5). C-type natriuretic peptide and natriuretic peptide receptor 2 are potent stimulators of endochondral ossification; their reduced expression resulting in severe dwarfism (6, 7).

GH production rates more than double during human puberty (8) with the consequent increase in IGF-I. In conjunction with sex steroids and insulin—which also increase physiologically in this period, these hormones produce an "anabolic cocktail" that results in rapid linear growth, increased muscle mass, increased bone mass accrual, and in the transformation of a child from a small prepubertal body into a fully grown individual with reproductive maturity. Peak height velocity coincides with peak GH production (8), and the deceleration in growth observed at the end of puberty in both sexes corresponds to the decrease in GH production rates (and IGF-I) characteristic of that period (Fig. 1). Although linear growth and adult height are virtually complete by 14.5-15 years in females and 16.5-17 years in males, the bodily changes continue and muscle mass and strength, as well as peak bone mass, are not fully achieved until early to mid 20s in girls and mid to late 20s in males (9).

Administration of testosterone in males and estrogen in girls causes significant augmentation of GH production in children (8, 10, 11). These effects on GH are blocked in boys by tamoxifen, an estrogen receptor blocker (12), and administration of a nonaromatizable androgen, oxandrolone, results in no detectable increase in GH production (10). Nonaromatizable androgens stimulate linear growth (13, 14), likely via their anabolic effects at the epiphyseal growth plate (15-17) through the androgen receptor by modulation of the hypertrophic zone differentiation and chondrocyte proliferation (16).

### ESSENTIAL POINTS

- Starting use of growth-promoting therapy such as growth hormone (GH) in children in puberty greatly limits time available for growth
- Estrogen is the principal modulator of epiphyseal fusion even in males
- Nonaromatizable androgens directly stimulate longitudinal bone growth
- High-dose GH, and use of gonadotropin-releasing hormone analogues in combination with GH, both can promote taller growth in puberty, in boys and girls; high cost and the suppression of physiologic puberty can hinder their use
- Aromatase inhibitors block estrogen and increase testosterone production, slowing down growth plate fusion while promoting growth and lean body mass accrual in males
- Extensive data have accumulated in the last 20 years on the safety and efficacy of the use of aromatase inhibitors in male children, increasing height potential ~ 4 to 5 cm when used as monotherapy, and ~9cm when used in combination with GH for at least 2 years
- Aromatase inhibitors are a strong consideration to promote growth in pubertal short males, especially in combination with GH

## Estrogen and Epiphyseal Fusion

Sex steroids have a dual effect on growth, stimulating rapid growth and increased GH production in puberty, but are also principally responsible for fusion of the growth plates in both males and females (Fig. 1). Two, now classical, prismatic cases of overgrowth in males greatly expanded our understanding of the process of epiphyseal fusion in humans. One by Smith et al (18), reported an adult male, 204 cm tall, fully virile, still growing at 28 years with a bone age of 15 years; gene sequencing showed a homozygous mutation in exon 2 of the estrogen receptor (ER) resulting in estrogen insensitivity. Morishima et al (19) reported a 24 year old male also 204 cm in height, with a bone age of 14 years with a homozygous mutation in exon IX of the CYP19 aromatase gene that resulted in severe aromatase deficiency. Hence, both estrogen insensitivity and estrogen deficiency resulted in delayed epiphyseal fusion and significantly tall height in males.

Estrogen has direct and indirect effects on the skeleton, increasing expression of osteoprotegerin, decreasing receptor activator of nuclear kappa B ligand and tumor necrosis factor α resulting in suppressed bone resorption (20). Estrogens induce commitment of precursors cells to osteoblast lineage and prevent apoptosis of osteoclasts (17, 20). ERα is the most abundant ER in bone (20). The signaling pathways of ERs are complex, some ligand dependent some ligand independent, and the latter can be influenced by circulating growth factors. However, estrogens also appear to be critical in endochondral ossification of the growth plate (resting, proliferative, and hypertrophic zones). Investigators studying proximal tibia of female mice with ERα knockout (KO), for example, showed increased growth plate height compared with wild type, and prolonged sustained longitudinal bone growth in the KOs (21), similar to the estrogen resistant man (18). This is true also in ERα collagen–specific KOs (20). Estradiol accelerates fusion of the growth plate in rabbits by advancing senescence of the growth plate via proliferative exhaustion of the chondrocytes (21), and estrogen decreases resting zone chondrocytes and

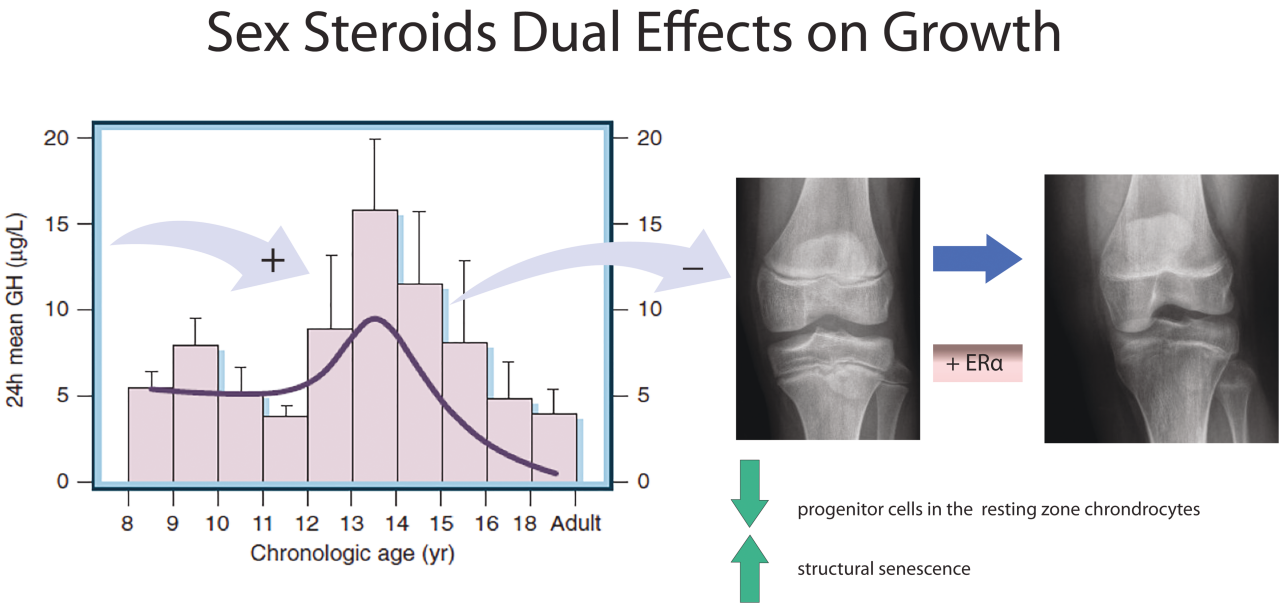



**Figure 1.** The histogram shows GH production rates for blood samples measured every 20 minutes for 24 hours in normal stature males aged 7-27 years across all 5 stages of puberty and young adulthood. The 50th percentile growth velocity curve for north American males is superimposed. (Redrawn with permission—from ref. (8)). The arrows indicate the dual impact of sex steroids depending on timing; the left (+) arrow implies the positive effect of estrogen enhancing GH production during puberty; the right (–) arrow represents the negative impact of continued estrogen exposure on growth, eventually fusing epiphyseal growth plates at the end of puberty. These physiologic effects of estrogen on the epiphyses are mediated via activation of the estrogen receptor alpha (ERα).

increases structural senescence (17, 21). Estrogen administration results in epiphyseal closure in aromatase-deficient men (22). In aggregate, a plethora of work both in experimental animals and humans has convincingly shown that estrogen, mediated via ERα, is the principal regulator of epiphyseal fusion in males and females.

## Short Stature in Puberty

About 87% of adult height is achieved prior to the onset of puberty, hence when using growth-promoting agents it is desirable to do so before sexual maturation begins. However, pediatric endocrinologists often face the dilemma of what to do when seeing, not infrequently for the first time, a growth-retarded patient at, or shorter than –2 SDS for height, who is well in the midst of puberty. Once proper diagnosis is established, considering intervention with a growth-promoting agent becomes challenging as the time window for linear growth is also closing. In patients with GH deficiency and those with idiopathic short stature there are therapeutic choices to be considered discussed below.

### Treatment Options For Growth Retardation In Puberty

#### High-dose GH

Conventional Food and Drug Administration (FDA)–approved GH doses used in GH deficiency range from 0.2 to 0.3 mg/kg/week given as a daily subcutaneous injection; lower doses are used in Europe and Australia. Given GH production rates more than double during human puberty, a logical consideration is whether high doses of GH can improve linear growth more than lower doses and result in taller adult height. In a pivotal trial conducted over 20 years ago (23), we compared linear growth responses in 97 short children with GH deficiency who had at least 6 months of prior GH therapy, randomly assigned to either conventional dose (0.3 mg/kg/week) vs high GH dose (0.7 mg/kg/week) given daily; 45 completed 36 months of treatment. After 36 months the high-dose group grew in aggregate +4.6 cm more than the conventional dose group, and after 4 years +5.7 cm more. These data led to FDA approval of high-dose GH in puberty (24). Taller heights with higher doses have been confirmed by others (25) suggesting a dose-dependent increase in height. The side effect profile of high doses was good, but median IGF-I concentrations were ~40% higher using high-dose GH (23). We now have a greater understanding of the need to maintain IGF-I concentrations within the normal range (26) which is challenging to do using very high doses. The cost of this approach is also largely prohibitive, hence this strategy, although feasible, should not be used routinely in adolescence, but instead only considered for those most growth retarded at the start of puberty (23, 27). When higher GH doses are used, IGF-I concentrations should be maintained within +2SD.

#### Suppression of puberty with GnRH analogues plus GH

To promote growth in pubertal short children another approach is to suppress puberty altogether while co-treating with GH. GnRHa in combination with GH has been used to promote growth in multiple clinical situations associated with poor linear growth when the children are in physiologic puberty. In 21 GH-deficient pubertal boys and girls, Mericq et al (28) compared results of treatment with GH alone vs GH and a GnRHa for 3 years. Combination treatment resulted in a gain of 12.3 cm in predicted height compared with 3.3 cm in those treated with GH alone, with near final height improving from –4.0 SDS in both groups to –2.7 SDS in the GH alone vs

**Table 1.** Gain in height in children using combination GH/GnRHa

| Condition | Reference | Age at start (years) | Years of treatment | Actual or predicted net height gain (cm) | Height SDS |
|---|---|---|---|---|---|
| GHD | Mericq (28) | 14.3 | 3 | + 3.3 GH<br>+12.3 GH/GnRHa | –4.0 baseline<br>–2.7 GH<br>–1.3 GH/GnRHa |
| SGA | Lem (29) | 12.2 | 2 | +13.6 (F)<br>+10.9 (M) | NA |
| SGA/ISS | Kamp (30) | 11.4-12.2 | 3 | +8.0 (F)<br>+10.4 (M) | NA |
| SHOX | Scalco (31) | 11.8 | 1.4- 5.8 | NA | –2.3 baseline<br>–1.7 GH/GnRHa |
| CPP | Pucarelli (32) | 9.9 | 2-4 | +2.3 GH<br>+8.2 GH/GnRHa | NA |

Abbreviations: F, female; GH, growth hormone; GnRH, gonadotropin-releasing hormone; M, male; NA, not available.

–1.3 SDS in the combination group (28). Comparable results were observed using combination GH and GnRHa treatment in children born small for gestational age (29, 30) and patients with SHOX haploinsufficiency (31). This improvement is also observed in those with precocious puberty and poor height potential (32, 33). Concomitant suppression of puberty and GH treatment results in a net gain of 5 to 10 cm in adult height (Table 1).

GnRHa use has not been associated with permanent detrimental effects on bone in children (34, 35). In girls with precocious puberty, bone mineral density Z scores can decrease during treatment but after treatment discontinuation bone mineral density is regained (35). Use of GnRHa as monotherapy in *normally timed* puberty, however, has been discouraged, as it may have a negative impact on bone mineralization (36), yet time-limited combination treatment with GH does not appear to have a detrimental effect on bone (37, 38). This approach to increase adult height while child is in puberty requires at least 2 years of combined treatment.

However, suppressing a *physiologically* timed puberty will render a pubertal child hypogonadal at a critical time in development. In this situation the child will not only be quite short, but also sexually infantile compared with his/her peers; the latter could have psychological implications for some children. Most data on the impact of GnRHa on mood and behavior come from its use in precocious puberty and studies have shown conflicting results regarding the impact of precocious puberty and its treatment on psychosocial metrics. Some have linked GnRHa use to higher rates of depression, suicidal thoughts, behavioral problems, and worse quality of life (QoL) than in girls with normally timed puberty (39-44). Others have failed to find any differences in self-image, self-esteem, or behavioral issues in children with precocious puberty when compared with healthy controls (35, 45, 46) and evidence regarding psychological benefit from GnRHa treatment of precocious puberty was inconclusive (33). However, when suppressing *normally timed* puberty with a GnRHa used in conjunction with GH, there appears to be no detrimental effects on psychosocial function (47, 48). More research in this area is needed.

We had previously shown that suppression of the GnRH axis with a GnRHa in healthy eugonadal young men for even 10 weeks results in significant catabolic effects with suppression of whole-body protein synthesis, increased adiposity (49), and increased urinary calcium losses (50). Hence, risk/benefit assessment and willingness to postpone pubertal development need to be openly discussed prospectively with these young patients and their families.

### Aromatase inhibitors

The process of epiphyseal fusion in children is estrogen driven. In a severely short pubertal child, can we therefore be more selective than fully suppressing puberty? Aromatase P450 (estrogen synthetase), product of the CYP19 gene located on chromosome 15, catalyzes the conversion of C19 androgenic steroids (testosterone and androstenedione) to estrogens (estradiol and estrone). It is expressed in several tissues including ovary, adipose tissue, liver, muscle, bone, syncytiotrophoblast, and breast tumors. Potent, oral third generation aromatase inhibitors (AIs) are FDA-approved for postmenopausal women with metastatic breast cancer (51).

*(A) Pharmacology.* Anastrozole (1 mg), letrozole (2.5 mg), and exemestane (25 mg) each achieve potent tissue aromatase blockade, 96.7%, >99.1% and 97.9% respectively (52-55). Anastrozole and letrozole are reversible aromatase blockers mostly metabolized by the liver and administered orally without regard to food. Exemestane is a steroidal competitive analogue of androstenedione that causes irreversible blockade of tissue aromatase, absorption affected by fat contents, hence it must be administered with food. We have shown pharmacokinetics and pharmacodynamics were comparable in young males to those of postmenopausal women, with peak concentrations achieved ~1 hour after administration (56, 57). Using stable isotopes of leucine we directly compared the impact of full GnRH axis suppression vs selective estrogen blockade in healthy eugonadal young men (58). Data showed a substantial decrease in rates of whole-body protein synthesis and increased adiposity with GnRH suppression whereas no significant differences were detected in these metrics when only estrogen was suppressed (58), suggesting lack of catabolic effect at least during the window of the experiments.

*(B) Impact on linear growth.* AIs have been used to promote linear growth both as monotherapy and in combination with GH in boys with constitutional growth delay, GH deficiency,

**Table 2.** Studies using aromatase inhibitors in males for growth promotion

| Reference | Condition | Study type | N | Age (years) | Comparators | Rx Length | HTSSDS pre | HTSDS post | Gain in PAH or near final height (cm) | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Wickman (59) | CDGM | RCT | 23 | 15.1 | Testosterone/ letrozole<br>Testosterone/ placebo | 1 year | NA | NA | +5.1<br>No gain | |
| Hero (60) | ISS | RCT | 31 | 9-14.5 | Letrozole<br>Placebo | 2 years | –2.3<br>–2.4 | +0.7*<br>No gain | +5.9<br>No gain | *SDS for BA<br>No adult HT gains in prepubertal patients (61) |
| Mauras (62) | GHD | RCT | 52 | 14.1 | GH/anastrozole<br>GH/placebo | 3 years | –1.4[a]<br>–1.5[a] | +0.77** | +4.5 (2 years)<br>+6.7 (3 years)<br>+1.0 (2 years)<br>+1.0 (3 years) | [a]Patients on GH at baseline<br>HT gains from baseline<br>**>than PL |
| Mauras (63) | ISS | RCT | 76 | 14.1 | AI (anastrozole/ letrozole)<br>GH<br>GH/AI | 2-3 years | –2.2<br>–2.4<br>–2.3 | –1.73 (24 months)<br>–1.43 (24 months)<br>–1.25 (24 months) | +5.2<br>+7.6<br>+9.5 | Gains vs historical controls (CDC) |
| Rothenbuhler (64) | ISS | Retrospective | 24 | 15.2 | GH<br>GH/anastrozole | 11.5 months<br>19 months | –1.70<br>–1.70 | –1.8<br>–1.1 | +4.1<br>+8.3 | Gains vs historical controls |
| Miller (65) | GHD/ISS | Retrospective | 142 | 12.1/10.76 | GH/AI | 2 years | –0.99/–1.04 | –0.40/–0.65 | NA | Gains from baseline |
| Salehpour (66) | CDGM | RCT | 91 | 12.6-14.6 | Letrozole<br>Oxandrolone<br>Placebo | 2 years | –2.91<br>–3.0<br>–2.88 | –2.27<br>–2.37<br>–2.86 | +6.1<br>+1.9<br>+1.4 | Gains from baseline |
| Leschek (67) | FMPP | Prospective: no control | 28 | 4.9 | Testolactone/ anastrozole + spironolactone | 7.3 | –1.5<br>Predicted adult HT | –0.3<br>Actual adult HT | +8.9cm | Bone age at baseline 9.7 years |

Abbreviations: AI, aromatase inhibitor; CDC, Centers for Disease Control; CDGM, constitutional delay growth and maturation; FMPP, familial male-limited precocious puberty; GH, growth hormone; HT, height; LT, letrozole; PL, placebo; RCT, randomized clinical trial; .

idiopathic short stature, and other conditions. Prospective trials conducted are here discussed and summarized (Table 2).

In participants characterized as having "constitutional growth delay," Wickman et al (59) treated 23 boys with testosterone and either letrozole (2.5 mg) or placebo for 12 months. Those receiving testosterone/letrozole had a marked decrease in bone age acceleration advancing +0.9 bone age years in 18 months vs +1.7 years in the testosterone/placebo group. This resulted in +5.1 cm increase in predicted adult height using the AI vs no change with placebo at 18 months. These investigators further reported their experience using letrozole (2.5 mg) vs placebo in 31 boys aged 9-14.5 years with idiopathic short stature (ISS). Those receiving letrozole as monotherapy had a marked slowdown of bone age acceleration of +1.24 vs +2.05 years in the placebo group (61), resulting in an increase in predicted adult height of +5.9 cm at 2 years in the AI vs no change in the placebo group. There were 27/31 prepubertal boys at study entry (60). Long-term follow-up of 20 of these boys showed no differences in adult height between the groups using letrozole as monotherapy (61). Most of these boys were still prepubertal at the end of 2 years treatment with bone ages of approximately 10 years (61), suggesting that administration of an AI as monotherapy is not useful to promote growth in prepuberty.

In a randomized controlled trial we used AIs in combination with GH in 52 very short boys (height SDS –2.3) with GH deficiency (mean age 14.1 ± 0.1 years) who were in full puberty and on GH treatment for at least 6 months (62). Boys were randomly assigned to continue GH plus either anastrozole or placebo for up to 3 years, or whenever they finished growing (62). Bone age advancement after 2 years of treatment was +1.8 and +2.7 years in the anastrozole vs placebo groups and after 3 years +2.5 and +4.1 years, respectively. Net gain in predicted adult height was +4.5 cm after 24 months and +6.7 cm after 36 months in the GH/anastrozole group vs +1.0 cm in the GH/placebo group at each of the same time points. The safety profile was excellent (see below).

We subsequently studied a group of 76 boys with ISS (height SDS –2.3 ± 0.0 SDS) who were in puberty (mean testosterone 223 ± 22 ng/dL (7.74 ± 0.76 nmol/L) but had residual height potential by bone age (63). Participants were randomly assigned to either AI alone (anastrozole [1 mg] or letrozole [2.5 mg]), GH alone (0.3 mg/kg/week given subcutaneously daily), or combination AI/GH for at least 24 months. Those with residual height potential at 24 months continued treatment for 12 more months (36 months total); patients were followed for 12 additional months after study drug discontinuation to assess their near-adult height. After 24 months administration of an AI, either alone or in combination with GH resulted in a marked slowdown of the tempo of bone age acceleration and a net height gain of +14.0 ± 0.8, +17.1 ± 0.9, and +18.9 ± 0.8 cm from baseline (Fig. 2A), and height SDS improvement to –1.73 ± 0.12, –1.43 ± 0.14, and –1.25 ± 0.12 after AI, GH, AI/GH, respectively (Fig. 2B). This compares favorably with the expected net gain in mean height gain of +10.2 ± 0.8 cm for adolescent boys with a height SDS of –2.0 between 14 and 16 years old based on Centers for Disease Control data (68). Those treated for 36 months grew more. The absolute change in height from baseline at near-final height was highly significant within groups: AI +18.2 ± 1.6 cm; GH, +20.6 ± 1.5 cm; AI/GH +22.5 ± 1.4 cm whereas the expected height gain in boys with height of –2.0 SDS was +13.0 cm in the same time period (63). Hence, when boys with severe ISS naïve to treatment who are also in the midst of puberty are treated with either an AI, GH, or AI/GH for 2 years the height gains are approximately 4 cm, 7 cm, and 9 cm, and gains at near-final height are 5.2 cm, 7.6 cm, and 9.5 cm, respectively (Fig. 3). IGF-I concentrations do not increase significantly with AI monotherapy whereas they increase as expected with the GH and GH/AI combination (63).

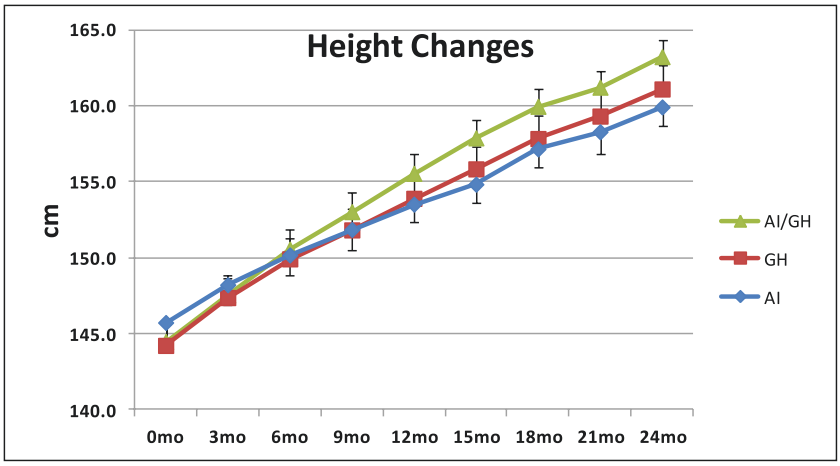
In the above-mentioned studies, subjects had bone ages <14 years at study entry. Rothenbuhler et al (64) pushed these boundaries further and explored using AIs in 24 boys with ISS and advanced bone ages of >14.5 years treated by their clinicians to receive GH alone (average length of treatment 11.5 months) or GH/anastrozole (average 19 months). The authors report achieved height gains of +4.1 cm with GH and +8.4 cm with combination anastrozole/GH compared with historical controls (64).

A retrospective chart review of 27 pubertal boys treated with an AI alone reported no increase in height prediction after 21 months (69); however, this was not a randomized prospective trial, patients were not particularly short (height SDS –1.1) and specific diagnosis for the children were not available. Miller et al (65), on the other hand, investigated "real-world" use of AIs outside the confines of a clinical trial in a retrospective, observational database (ANSWER program). They report height outcomes of 142 short boys naïve to GH therapy who were in puberty (115 GH deficient, 27 ISS) with heights of –2.0/–2.2 SDS in GH-deficient/ISS groups, respectively. After 2 years of clinical treatment with combination AI/GH height outcomes were –0.40/–0.65 SDS for the GH-deficient and ISS groups, respectively. The safety profile was very good during this treatment window.

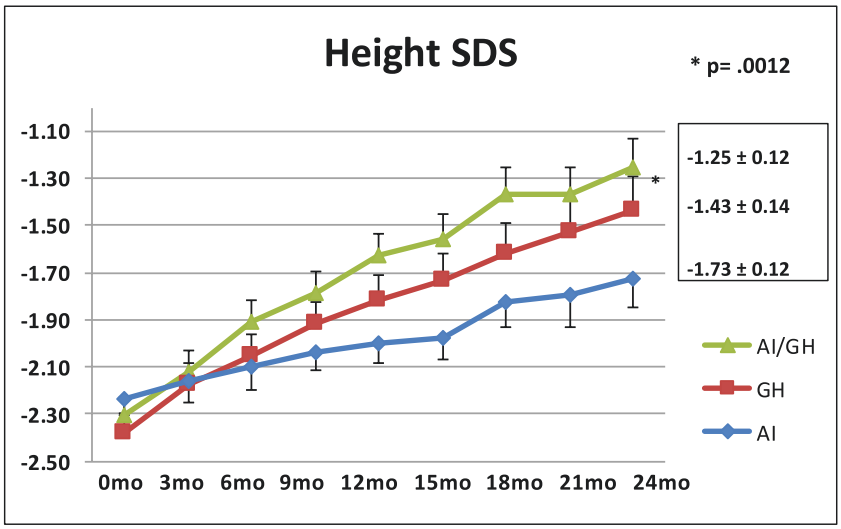
Another model using AIs as monotherapy was reported in a clinical trial of 91 boys with constitutional delay of growth and puberty (12.6-14.6 years), where subjects were randomized to receive either letrozole, oxandrolone, or placebo for 2 years (66). An increase in predicted adult height of +6.1 cm with letrozole, +1.9 cm with oxandrolone, and +1.4 cm with placebo was observed.

Of note, predicted adult height based on X-ray data may not necessarily correlate with actual adult height in pathological disorders of growth, hence caution should be exercised when using bone age data as this assumes normal growth which a given patient may or not be sustaining (70, 71).

*(C) Impact on bone.* Estrogen blockade, if prolonged, can negatively impact bone mineralization. Estrogen-deficient and -insensitive men were noted to have severe osteopenia/osteoporosis (18, 19); however, these men had life-long congenital estrogen deficiency, a situation not directly comparable with time-limited blockade. Boys with ISS using letrozole as monotherapy had decreased bone resorption markers during treatment suggesting that AI when used alone suppressed bone turnover possibly through an androgen-mediated effect (72). Some of these children had spine magnetic resonance imaging after 2 years and those receiving letrozole were initially reported to have a variety of vertebral irregularities (73); however, long-term follow-up data showed frequency of subjects with vertebral anomalies to be the same in both letrozole and placebo groups (61). In the randomized comparator study of boys with ISS (63), we carefully and prospectively assessed bone mineral density accrual by dual-emission X-ray absorptiometry (DEXA) including lateral spine to assess bone morphology, disk space narrowing, wedging, compression, and overall vertebral




(a)




(b)

**Figure 2.** (A) Changes in absolute height gain over 24 months in the groups treated with AIs, GH, and AI/GH ($P < .006$) (data contained in ref. (63)). (B) Changes in mean (SE) height SDS (top panel) over 24 months in the same groups. *$P < .0012$ (Redrawn with permission from ref. (63)).

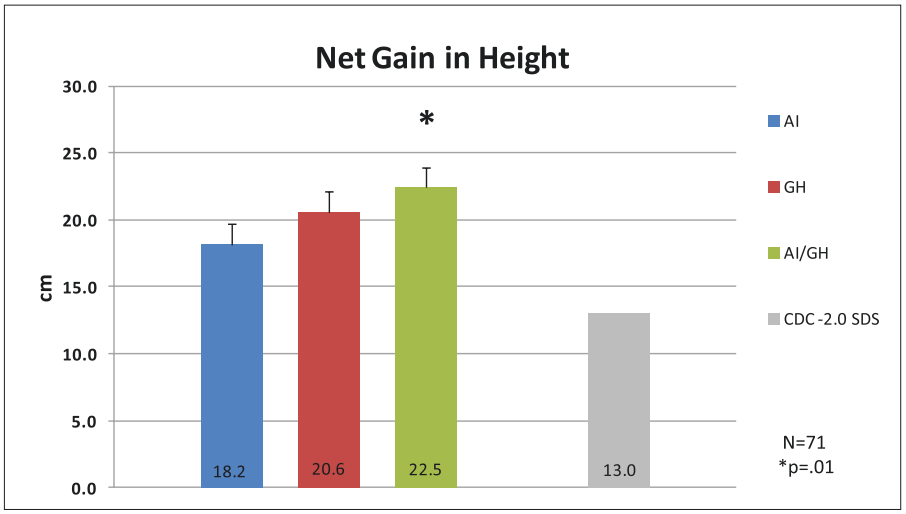



**Figure 3.** Net gain in height (cm) in the same three groups AI, GH, AI/GH (*$P = .01$ among groups; **$P = .002$ between AI and AI/GH groups). Average height and net gain in height of young men of similar ages with height SDS −2.0 are shown for comparison on the far right bars (Center for Disease Control data). (Redrawn with permission from ref. (63)).

irregularities. A bone questionnaire was used to assess bone pain, at baseline, and yearly for 2 years. Lumbar spine bone mineral density (reflective of trabecular bone) remained within normal range in the 3 groups for 24 months after correction for height, although the AI alone group had the lowest SDS of the 3 groups (–1.06 SDS); corrected whole-body bone mineral density (reflective mostly of cortical bone) was initially low but remained constant in the 3 groups as well (63). Data showed comparable results among the AI, GH, and AI/GH groups in vertebral findings, some of which were present at baseline, and some no longer detected as treatment progressed (63). The extent of these abnormalities was indeed very mild and was similar to those commonly seen in short adolescents (74, 75). Frequency of bone fractures were the same among AI, GH, or combination groups after 3 years (63). In aggregate, data show that when used for 2 to 3 years in males with physiologically timed puberty there appears to be no negative impact on bone health. These investigators, nonetheless, deem it prudent to obtain a DEXA scan of the lumbar spine prior to deciding whether to initiate therapy with an AI in a pubertal adolescent to assess the presence of osteopenia. This also allows careful prospective follow-up of those with any meaningful deficits in bone mineralization for age.

*(D) Impact on cognition and quality of life.* Limited data exist on the effects of estrogen suppression in boys on cognitive function. Finish investigators performed the only reported study in age-appropriate cognitive testing in boys with ISS treated with letrozole vs placebo for 2 years and observed no detectable differences in cognitive performance IQ between the groups (76).

The QoL in Short Stature Youth is a questionnaire administered to both patients and parents/caregivers developed and validated by Bullinger et al (77) to assess physical, social, emotional domains, and total scores in children with severe short stature. All 76 participants and their parents/caregivers completed this survey in the comparator study of pubertal boys with ISS yearly over 2 years (78). From the patients' perspective there were detectable improvements in measures of QoL in all domains in the GH alone and AI/GH groups, but not those using only AI, whereas the parents/caregivers in all 3 treatment arms reported improvements in all domains after 2 years (78).

*(E) Impact on fertility and sperm.* Men with congenital estrogen deficiency have been reported to have decreased fertility with reduced sperm viability (18), and both male and female mice with disrupted ERα are infertile (79). However, time-limited aromatase blockade has different effects in men (80). Impact of AIs on sperm production and motility has been studied in young men who previously received up to 3 years of GH with either placebo or anastrozole (81). Compared with those who previously received GH/placebo and with healthy age-matched controls, there were no differences in sperm counts or motility at least 2 years after treatment discontinuation (81). Aromatase blockade causes a drop in estradiol and a marked rise (~50%) in testosterone concentrations, yet still mostly within normal range (62, 63). Shoshany et al (82) reported the use of anastrozole in 86 oligospermic hypogonadal men was associated with improved testosterone/estradiol ratio and 25% showed improved sperm production. Overweight/obese subfertile men increased testosterone levels and improved sperm production with anastrozole, 46% of whom achieved pregnancy (83). By also increasing gonadotropins AIs have been used in the treatment of subfertile men of different etiologies with some encouraging results (82-87).

*(F) Impact on body composition.* There is a common observation of overall increased musculature in adolescent boys taking AIs with or without GH. Although firm data on their exercise enhancing effects are lacking, both AIs and GH are considered "ergogenic" and banned by the World Anti-Doping Agency in athletic competition (88). AIs results in quantifiable increases in lean body mass accrual in men. When given for 24 months to adolescent boys (63), despite comparable fat free mass at baseline, the net gain in lean body mass was significantly higher in those treated with combination AI/GH (+15.2 kg) vs AI alone (+11.3 kg) vs GH (+11.8 kg). These effects have been largely welcomed by young patients most of whom were quite small and with poorly developed musculature prior to treatment.

*(G) Other safety considerations with AIs.* As stated above the degree of tissue aromatase blockade is quite strong (>95%) for all 3 available drugs, yet letrozole is clearly more potent than anastrozole and exemestane with >99% tissue suppression (53-55). This difference in potency has not translated into differences in disease survival in women with breast cancer (55). In boys letrozole can cause a supraphysiological rise in testosterone (60), and letrozole causes ~25% greater rise in testosterone than anastrozole (63). Although most values are still well within normal range letrozole can more commonly lead to supraphysiological concentrations of testosterone. Given that anastrozole has had strong positive results when used to promote growth, particularly in combination with GH, it is these investigators' preference to use anastrozole clinically, monitoring testosterone and estradiol liquid chromatography mass spectrometry mass spectrometry (LCMSMS) concentrations while on therapy.

Besides items B to F above, children participating in institutional review board–approved clinical trials had adverse events carefully recorded. Most common were musculoskeletal complaints (fractures or ligament trauma during sports) and were similar to control or comparator groups without implication of causality. Plasma lipids, liver function tests, general chemistries, and blood counts have not been negatively altered by AIs during the 2- to 3-year window of time used (60, 62, 63, 89). Insulin sensitivity is not adversely affected by AIs in males, with the increase of lean body mass observed a positive effect for insulin sensitivity. Although not quantified by scale the rise in testosterone caused by AI use can exacerbate acne which can be treated topically and does not typically result in discontinuation of the medication. In trials of 52 and 76 boys followed for up to 3 years (62, 63), no serious adverse events were attributed to use of AIs.

## Other Conditions That Limit Growth in Puberty

Familial male-limited precocious puberty, also known as testotoxicosis, is a rare form of precocious puberty due to a gene mutation resulting in constitutive activation of the luteinizing hormone receptor independent of gonadotropins. These boys typically present between ages 4 and 6 years

with striking virilization and pubertal testosterone concentrations, fast linear growth and often tall stature for age and a marked advancement of skeletal maturation, leading, untreated, to significantly short adult height. Leschek et al (67) reported the National Institutes of Health experience treating 28 of these boys, mean age 4.9 ± 1.5 years, bone age 9.7 ± 3.5 years, using earlier generation of a weak aromatase inhibitor (testolactone), later switched to anastrozole, along with a weak androgen blocker, spironolactone. Mean treatment duration of 7.3 years resulted in achievement of a normal adult height (173.6 ± 6.8 cm; –0.4SDS) (67). The marked slowdown in skeletal maturation caused by the AI and the increase in growth caused by the nonaromatizable androgen are largely responsible for this response. At present, anastrozole and bicalutamide—a more potent androgen receptor blocker—can be used successfully in this condition (90). Familial male-limited precocious puberty represents the longest continuous exposure to AIs in boys to promote growth to date. Safety profile has been excellent.

AI use has been reported in a variety of miscellaneous conditions with either advanced bone age, poor height potential or hypogonadism. In adrenal hyperplasia anastrozole was reported to slow down bone age maturation after 5 years of use (91). Interestingly, this cohort of children ranged from 3.2 to 13.9 years of age and none had gonadal puberty at initiation of the AI monotherapy (91), underscoring the impact of aromatization of adrenal androgens in advancing the bone age. Exemestane use in a single case report of adrenal hyperplasia with a 7 year advanced bone age was reported increase height potential (92). In a small group of 12 severely obese hypogonadal men use of once-a-week letrozole was reported to increase serum testosterone to the normal range (93). Although encouraging, these data are limited, and more research is needed in larger groups of patients before firm recommendations are made in these conditions.

## What About Use of AIs in Girls?

Use of AIs to promote growth in females with physiologically timed puberty has been limited. Contrary to pubertal boys in whom suppressing estrogen slows down bone maturation and promotes growth, yet allows them to continue to virilize, blocking estrogen production in pubertal girls would lead to suppression of the changes in puberty altogether, with unknown effects on bone maturation and density. The expected increase in testosterone and androstenedione could in theory cause mild hirsutism and acne. There is also the theoretical concern, through the gonadotropin increase observed with AIs, of increased ovarian cyst formation, the principal reason for the lack of use of this class of compounds in premenopausal women with breast cancer. However, the rise in gonadotropins caused by AIs makes them a practical treatment for ovulation induction in females (94, 95). AIs (anastrozole and letrozole) have been used in McCune Albright syndrome, a condition of gonadotropin-independent precocious puberty due to a somatic mutation that activates the alpha subunit of the stimulatory G protein. These girls have recurrent ovarian cysts and high ovarian estrogen production. The results using AIs for control of the disease have been mixed, with anastrozole deemed ineffective at halting ovarian cyst formation and bone age progression in a prospective trial of 28 girls with McCune Albright syndrome for 1 year (96), whereas retrospective analysis of response to letrozole when used for up to 6 years in 28 girls with this disorder was found to be highly effective reducing bone maturation and increasing adult height potential (97). These differences may relate to the type of study (prospective randomized vs retrospective), the relative potency of the AI used (anastrozole vs letrozole), and the marked heterogeneity of the clinical course in this condition.

Papadimitriou et al (98) studied 40 girls with early central puberty between 7.5 and 9 years of age with bone age advanced by 1.8 years. Girls were randomized to either monthly leuprorelin alone or with anastrozole for 2 years or up to 10 years of age. They reported a predicted adult height gain at 24 months of +1.21 ± 0.45 SDS (7.51 cm) with combination treatment, vs +0.31 ± 0.37 SDS (1.92 cm) with leuprorelin alone. The rationale was to better suppress not only gonadal estrogens but peripheral estrogens generated from adrenal precursors. They reported no virilization and a good safety profile. However, ovarian morphology was not assessed. More studies in this patient population are needed.

## Practical Considerations: Clinical Pearls

In both very short girls and very short boys the assessment of puberty status and skeletal maturation become critical factors in the decision of how best to promote growth. First, there should be a thorough assessment and discussion with the family and patient regarding therapeutic choices. In girls, suppression of physiologically timed puberty using a GnRHa can be considered in conjunction with GH. These could be started concomitantly or in tandem. Not only the linear growth per se, but the tempo of bone age acceleration would need monitoring, with bone ages repeated at 6-month intervals while on combined therapy.

In pubertal short boys we and others have been using aromatase inhibitors to promote linear growth for over 20 years and have painstakingly investigated their pharmacology, metabolic effects, and linear growth effects in detailed, well-controlled, and laborious studies. The impact of AIs on bone, linear growth, sperm production, and QoL has been thoughtfully studied in children with overall positive results. Neither plasma lipids nor insulin sensitivity have been adversely affected by their use and although acne may worsen in some, in our experience this has not been a hindrance for their use. Overall, AIs are a strong consideration to use in boys with severe short stature (height SDS <–2) who are well amid puberty (not in prepubertal children) with a bone age of at least >12 years. We prefer to use AIs in combination with GH as it has the most robust effect enhancing linear growth. We also prefer to use in boys whose bone age shows residual height potential, namely <14.5 years and not in those with a bone age >15 years. It is our practice to obtain a testosterone and estradiol (LCMSMS) prior to initiation, as well as a bone age and lumbar and whole-body DEXA—the latter to include body composition assessment. If the Z score of the lumbar spine is <–2.0 SDS we either do not use AI, or, if used, follow very carefully with yearly bone densitometry exams to avoid further worsening of the osteopenia. We prefer to use anastrozole (1 mg daily) instead of letrozole as the rise in testosterone is not as severe and the degree of tissue aromatase good enough to accomplish the desired slowdown in bone age acceleration and increased height potential. We typically use AIs for no more than 3 years in those with physiologic puberty as that is the extent of the data safety we have in these patients. If co-treating with GH we also monitor IGF-I.

We do not at present endorse the use of AIs in otherwise normal girls with either precocious or physiologic puberty to promote linear growth; girls with McCune Albright syndrome represent a separate exception.

This class of drugs—including anastrozole, letrozole, and exemestane—are now generic in the United States, hence manufacturers and specific uses for AIs included in this review are not in these products' labels. However, the American Academy of Pediatrics Policy Statement (99) on the off-label use of drugs in children states that the term "off label" does not imply an improper, illegal, contraindicated, or investigational use. Absence of labeling for a specific age group or specific disorder does not necessarily mean the drug use is improper, and the use of drugs can be justified if strong clinical efficacy and safety data back their use in children. We believe this is the case for AIs in disorders of growth in young males in puberty. Future studies to optimize dosing, and continuing to monitor long-term outcomes are needed.

## Conclusions

Growth-retarded children that present in puberty represent both a diagnostic and therapeutic dilemma. The most common etiologies, GH deficiency, and, if all other pathologies are excluded, ISS, can be treated with GH, the last one at least in the United States, but the relentless acceleration of bone age that occurs in puberty greatly limits height potential and the time available for growth. This often necessitates a different strategy, and, in this review, we acknowledge that therapies discussed may not be readily available in all countries. High-dose GH is a possibility but adds considerable expense and likely would increase IGF-I to supraphysiologic levels. We believe high GH doses should be used rarely, and must be reserved solely for those most growth retarded at the start of puberty and only if lower doses fail to achieve desired growth outcomes and with very careful monitoring of the IGF-I. Complete GnRH axis suppression along with GH is a proven positive alternative in both boys and girls, but would render these adolescents hypogonadal at a critical time of development, which calls for open discussion with the patient and the family. On the other hand, attempting to use a growth-promoting hormone like GH for the first time in the midst of puberty without also addressing the tempo of epiphyseal fusion will likely not maximize height potential. GnRHa in combination with GH, we believe, should only be considered in very short pubertal patients with limited height potential, particularly in pubertal girls or in boys for whom AIs are not a treatment option.

AIs which selectively and potently suppress estrogen while allowing the continued production and action of testosterone to promote virilization are a compelling alternative in pubertal males as they promote a slowdown bone maturation and increase height potential. Judicious use of AIs combined with GH, for 2 to 3 years, offers an alternative to the treatment of pubertal males with GH deficiency and with ISS with an excellent safety profile. Improved QoL measures were observed with combination treatment. Testosterone, IGF-I, and bone densitometry should be monitored while on treatment. Anastrozole is better than letrozole in avoiding excessive increase in testosterone. Treatment with AIs in physiologic puberty should be limited to 2 to 3 years.

Ultimately the best approach for children with growth retardation is early referral to pediatric endocrinology, well before the onset of puberty, so proper diagnoses are made and tailored interventions started. In all growth-promoting therapeutic options in puberty studied thus far—GH, GnRHa, and AIs, alone or in combination, intervention typically requires at least 2 years of treatment. While these therapies offer hope and an alternative to improve growth in very short pubertal children, careful discussion of these treatments and realistic expectations need to be discussed with families.

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