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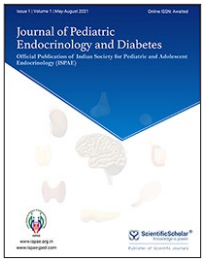

Invited Editorial Commentary

Aromatase inhibitors for idiopathic short stature: A Commentary

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The current paper addresses a management strategy to increase adult height in the case of normal variant or idiopathic short stature.[1] However, we believe that an important question to be addressed is that of the intrinsic value and social significance of seeking greater height as a desirable commodity. It also questions the methodologies that may be utilized in attempting to achieve these outcomes.

Final height in humans is, in part, determined by the timing of and rate of epiphyseal closure which, in turn, occurs through the action of estrogen on the epiphyseal growth plate. Estrogen promotes growth plate activity, regulates chondrocyte differentiation, and eventually leads to growth plate fusion. Aromatase inhibitors, by reducing the conversion of androgens to estrogens, are hypothesized to delay epiphyseal plate closure and potentially increase final adult height. Their use has been explored as a potential intervention for short stature in children and adolescents. The use of third-generation aromatase inhibitors such as letrozole and anastrozole remains experimental. In conditions where bone age is severely advanced due to the effect of prolonged exposure to sex hormones during childhood, such as late presentation of central precocious puberty, gonadotropin-independent precocious puberty, or congenital adrenal hyperplasia, rapid skeletal maturation leads to very early closure of epiphyseal growth plates and markedly truncated final adult height. Aromatase inhibitors may be considered in these circumstances, in combination with anti-androgens and tamoxifen (a selective estrogen receptor modulator). However, for individuals without an underlying medical condition and associated hormone imbalance (such as in idiopathic short stature), the use of aromatase inhibitors raises important ethical and medical considerations.

Specifically, there is growing concern about the use of pharmacological interventions (including growth hormone) aiming to augment height beyond a child's genetic potential. In 2009, the European Society of Pediatric Endocrinology recommendation on the use of gonadotropin-releasing hormone agonists in combination with growth hormone, stated that evidence of safety and efficacy was lacking and the use of these preparations was not supported by any major endocrine society worldwide.[2] Similarly, in 2017, the Australasian Pediatric Endocrine Group published recommendations on short stature and pubertal delay as part of the Australian Commission on Safety and Quality in Health Care.[3] Their recommendation concerning the use of aromatase inhibitors called for more evidence on safety and efficacy before routine prescription for children with short stature could be supported.

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Little evidence has emerged that the use of aromatase inhibitors improves final height;[4] however, when the data are reviewed, the purported evidence appears trivia.[5] Many studies followed participants for 1–2 years with insufficient data regarding the final adult height achieved. In an early study, Hero *et al*. reported a 5.9 cm increase in predicted adult height for the group treated with letrozole.[6] However, a follow-up study completed 4 years later indicated that there was no longer a significant difference in median adult height predictions between groups.

In the most recent systematic review and meta-analysis of aromatase inhibitor use in short stature (Liu *et al*.), 14 studies with 388 participants were reviewed.[7] The authors reported an increase in final height of 2.46 cm (mean difference) and an increase of only 0.34 cm predicted adult height (mean difference), both quoted as significant. Predicted adult height was based on mid-parental height and, hence, genetic expectation. Adverse events were 3 times as common in the intervention group, with an odds ratio of 3.1. While some studies have shown a small increase in height during adolescence, the impact on final adult height is minimal; individuals with short stature will still meet their familial expectations not impacted by this intervention.

Concerns remain about safety, with vertebral abnormalities seen in both animal models and pre-pubertal males, suggesting that aromatase inhibitor treatment during adolescence may impair the strength of growing vertebral bodies rich in trabecular bone.[8-11] In addition, risks of erythrocytosis (from supraphysiological levels of testosterone) and lowering of high-density lipoprotein cholesterol have been reported, although this is unlikely to be of clinical significance due to the duration of use for this purpose.

Society's disproportionate emphasis on stature often overlooks the broader aspects of health and well-being, which may lead to unnecessary medicalization of natural variations in height. There are a number of questions that need to be carefully considered and addressed when outlining any new potential medical intervention. These apply to the use of aromatase inhibitors to improve final height, as well as many other clinical situations.

The rationale for advocating for height increase in cases of idiopathic short stature or familial short stature must be carefully examined by all involved parties. What are the motivations behind the request, and who is driving it? Is the goal to enhance future career prospects, personal relationships, or overall quality of life? The expectations of all parties, including the individual, their family, and other clinicians, must be taken into account. This is frequently far more complex than a superficial consultation might suggest and may involve covert factors of secondary gain, more attention for the child, or even financial considerations. The belief that increased stature will lead to higher income or better attainment in society remains prevalent.

We stress the importance of presenting reality and addressing the question of stature as a commodity with perceived benefits that are unlikely to be realized in real-life terms. The clinician should strive to understand what a potential maximum increase in height of 2–4 cm means to the individual (or community) both now and in the future. It is imperative not to offer unrealistic hopes with disappointed outcomes to vulnerable individuals. In addition, families should be cautioned not to compare the child to others with excess weight gain driving prepubertal growth, an increasingly common reason for concerns regarding the growth of perfectly normal children.

Previous population studies from the UK on the use of growth hormone and its impact on psychosocial outcomes did not indicate any benefits from a small increase in final height. We are concerned about extending the rationale for the use of aromatase inhibitors in specific cases to include idiopathic short stature. There is a distinct difference between addressing abnormalities caused by prolonged excess of sex hormones, which accelerates epiphyseal closure and attempting to alter a normal pubertal process.

Finally, the current emphasis on a concept of greater height somehow resulting in improved life prospects would be better directed toward the importance of addressing the root causes of short stature. These include multigenerational pre- and postnatal nutritional deficiency, psychosocial deprivation, and chronic inflammatory disease (that is not infrequently subclinical). Embracing height variations should contribute to, rather than detract from, the diversity of the human experience.

REFERENCES

1. Dutta D, Agrawal R, Joshi A, Sharma M. Efficacy and safety of aromatase inhibitors in the management of idiopathic short stature: A meta-analysis. J Pediatr Endocrinol Diabet 2024;4:21-30.
2. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, *et al*. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752-62.
3. Australasian Paediatric Endocrine Group. 5. Do not routinely prescribe aromatase inhibitors to promote growth in children with short stature; 2017.
4. Mauras N, Ross JL, Gagliardi P, Yu YM, Hossain J, Permuy J, *et al*. Randomized trial of aromatase inhibitors, growth hormone, or combination in pubertal boys with idiopathic, short stature. J Clin Endocrinol Metab 2016;101:4984-93.
5. Diaz-Thomas A, Shulman D. Use of aromatase inhibitors in children and adolescents: What's new? Curr Opin Pediatr 2010;22:501-7.

6. Hero M, Norjavaara E, Dunkel L. Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: A randomized controlled trial. J Clin Endocrinol Metab 2005;90:6396-402.
7. Liu J, Yin S, Luo Y, Bai X, Chen S, Yang H, *et al*. Treatment of short stature with aromatase inhibitors: A systematic review and meta-analysis. Horm Metab Res 2021;53:391-401.
8. McGrath N, O'Grady MJ. Aromatase inhibitors for short stature in male children and adolescents. Cochrane Database Syst Rev 2015;2015:Cd010888.
9. Bajpai A, Simm PJ, McPherson SJ, Russo VC, Azar WJ, Wark JD, *et al*. Peripubertal aromatase inhibition in male rats has adverse long-term effects on bone strength and growth and induces prostatic hyperplasia. J Endocrinol 2010;207:27-34.
10. Hero M, Mäkitie O, Kröger H, Nousiainen E, Toiviainen-Salo S, Dunkel L. Impact of aromatase inhibitor therapy on bone turnover, cortical bone growth and vertebral morphology in pre-and peripubertal boys with idiopathic short stature. Horm Res 2009;71:290-7.
11. Hero M, Toiviainen-Salo S, Wickman S, Mäkitie O, Dunkel L. Vertebral morphology in aromatase inhibitor-treated males with idiopathic short stature or constitutional delay of puberty. J Bone Miner Res 2010;25:1536-43.

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