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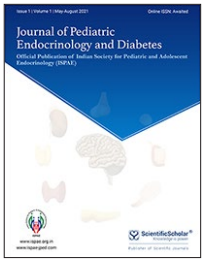

Invited Editorial Commentary

Delaying the growth plate closure to augment height

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Pediatric endocrinologists have always been embroiled in the quest for growth-promoting therapies to achieve an individual's full height potential or to augment height in many varied clinical scenarios. Besides growth hormone (GH) treatment, many other pharmacological agents have been investigated for efficacy and safety in promoting short-term growth, which is expected to translate into better adult height (AH). Gonadotropin-releasing hormone analogs (GnRHa) have established efficacy and safety in improving height outcomes in children with central precocious puberty. Testosterone has been used effectively in boys with constitutional delay in growth and puberty and oxandrolone in Turner syndrome.

The physis or growth plate is the cartilaginous portion at the end of long bones where longitudinal growth takes place. The growth plate has a complex structure and physiology and is influenced by endocrine and paracrine growth factors, cytokines, and other multiple signaling factors to promote linear growth. Estrogen is the primary factor causing closure and fusion of the epiphyseal growth plate in both males and females by promoting physeal dehiscence. There are many clinical observations that AH is dependent on the timing, duration, and level of circulating estrogens. Central precocious puberty left unattended results in short stature, whereas estrogen deficiency, especially in males, results in tall stature. Aromatase is a cytochrome P450, ubiquitous enzyme (CYP19A1 isoform) able to catalyze the rate-limiting step of conversion of androgens to estrogens. Estrogen in men is synthesized in peripheral tissues by local aromatase action on circulating androgens. Aromatase gene mutations highlighted the action of estrogen as one of the main regulators of bone maturation and closure of the growth plate. Men with congenital aromatase deficiency have tall stature associated with delayed fusion of the epiphyseal growth plate along with other features such as osteoporosis, overweight, glucose intolerance, hyperlipidemia, and reduction of fertility.[1] These observations led to the hypothesis that anti-estrogens may be a pharmacological tool to delay growth plate closure, thereby prolonging the duration both for linear growth and for interventions with other growth-promoting therapies, for example, GH treatment.

Anti-estrogens fall into two categories, selective estrogen receptor modulators (SERMs) and aromatase inhibitors. Anti-estrogens were therefore considered in the management of short stature from the late 1990s to 2000. Although there are very few published studies, SERMs like tamoxifen were used as off-label therapy to delay epiphyseal growth plate fusion in pubertal boys as monotherapy or along with GH therapy. In 2005, Kreher *et al*. published a retrospective review on pubertal boys who were treated with tamoxifen and concluded that tamoxifen significantly decreased the rate of skeletal maturation and increased the predicted AH without negative effects on sexual maturation.[2] Few anecdotal reports also exist on the efficacy of tamoxifen in augmenting height in pubertal boys. Even though studies on the negative effects of tamoxifen on

growth cartilage in experimental animals cannot be directly extrapolated to their short-term use in humans, SERMs were more or less abandoned for third-generation aromatase inhibitors such as letrozole and anastrozole, which have more acceptable safety profile.

Off-label use of aromatase inhibitors in pediatric endocrinology has been practiced for McCune–Albright syndrome and functional follicular ovarian cysts, familial male-limited precocious puberty, and Peutz–Jeghers syndrome with good clinical outcomes. Efficacy trials are yet to establish the usefulness of aromatase inhibitors in congenital adrenal hyperplasia and pubertal gynecomastia. Evidence from many studies in boys with short stature and/or pubertal delay suggests a positive effect of aromatase inhibitors on AH, but more long-term follow-up data are needed. A Cochrane database review by McGrath and O'Grady concluded that the "available evidence suggested that aromatase inhibitors improved short-term growth outcomes" but that there was no evidence to support an increase in final AH.[3] The use of aromatase inhibitors in prepubertal boys is not advised due to an association with vertebral deformities. Other safety concerns include a decrease in high-density lipoprotein-cholesterol levels and erythrocytosis.

As safety concerns are similar with letrozole and anastrozole, off-label use of these drugs based on the difference in potency would suggest that in boys with testotoxicosis and girls with McCune–Albright syndrome, letrozole might be more effective than anastrozole. Whereas, in boys with short stature, a less severe blockade of aromatase, as with anastrozole results in less elevated serum testosterone levels with higher attained height and possibly a milder effect on vertebral bone health.[4] The advantages of anastrozole, when compared with GnRHa in promoting height, are that anastrozole does not affect pubertal development and growth spurt. This will have positive effects on adolescent psychosexual development and peer group acceptance. Furthermore, bone mass accrual and body composition are less affected by aromatase inhibitors than by GnRHa. In a similar analogy, adding anastrozole to GH treatment for 2–3 years in boys who are still short at puberty onset, with GH deficiency or small for gestational age, may improve final AH.

In this journal issue, authors Dutta *et al*. have done a meta-analysis on the "Efficacy and safety of aromatase inhibitors in the management of idiopathic short stature (ISS)," providing key information on the use of these anti-estrogens in the management of short stature in pubertal boys.[5] Although there are limitations of non-uniformity and other misleading biases as short duration studies in these meta-analyses, every evidence based on published reports becomes important as it is unlikely that a large randomized control trial (RCT) continued until AH achieved will ever be carried out. Rothenbuhler *et al*., in 2015, published an RCT reporting the efficacy of a combination of rhGH and anastrozole started after puberty onset in boys with ISS to reach a greater AH than rhGH alone, supporting the use of aromatase inhibitors in pubertal boys with short stature.[6] Larger trials are needed to confirm this preliminary observation.

It should be remembered that children with ISS represent a highly heterogeneous group with multiple differing extrinsic and intrinsic growth plate defects, and as such, the response to hormonal or pharmacological intervention may be variable, influencing the study results even when the study is designed to tackle heterogeneity. Moreover, the lack of uniformity on age or pubertal stage at commencement and duration of treatment with aromatase inhibitors will result in variation in the treatment response and limit the comparability of the studies. Moreover, readers are reminded that the use of anti-estrogens in the management of short stature is only acceptable in pubertal boys, and as such, it may be pertinent to have this aspect included in the title of all such studies.

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