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Alternatives in the Treatment of Short Stature

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• Human recombinant insulin-like growth factor-1 • Metformin
• Low-dose androgens

Key points

- Gonadotropin-releasing hormone (GnRH) analogues may be useful in the treatment of short children with decreased growth potential due to early puberty in an attempt to delay pubertal progression.
- Aromatase inhibitors may prolong the growth period of short boys in puberty by inducing slower bone maturation.
- RhIGF-1 administration may be useful in the treatment of short children with growth hormone resistance or growth hormone inactivating antibodies. Its usefulness in the treatment of idiopathic short stature has, however, not been proven.
- Low-dose androgen therapy positively affects growth velocity, without affecting the tempo of puberty or final height, when used for short periods of time.

INTRODUCTION

New therapeutic alternatives for the treatment of otherwise healthy short children are clearly needed. Although human recombinant growth hormone (rhGH) treatment of idiopathic short stature (ISS) was approved by the US Food and Drug Administration years ago, it requires daily parenteral administration and its cost remains prohibitive in many parts of the world. Its

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effectiveness is particularly questionable in the case of healthy short children who enter puberty at a normal but relatively early age, in whom early bone maturation may lead to decreased lineal growth and growth potential.

In recent years, efforts have been made to find therapeutic alternatives that will allow for slower bone maturation and for more prolonged spontaneous or induced growth. In this article, the authors review the effects of gonadotropin-releasing hormone (GnRH) analogues (GnRHa) alone or in combination with rhGH and the use of aromatase inhibitors (AIs) on their own or in combination with rhGH as a means of delaying bone maturation and increasing the final height (FH) of this group of children.

Endocrine short stature may be due to growth hormone (GH) deficiency of hypothalamic-pituitary origin. However, it can also be secondary to abnormalities in the GH receptor, anomalies in the signal transduction between GH and its receptor, to abnormalities in the formation of the ternary complex formed by insulin growth factor-1 (IGF-1), the acid labile subunit (ALS) and binding proteins, or to abnormalities of the IGF-1 gene. These situations may lead to IGF-1 deficiency, which could potentially be treated more effectively with recombinant human insulin-like growth factor-1 (rhIGF-1).

Other treatment choices could include low-dose androgen therapy as a growth-promoting alternative for short peripubertal boys and metformin in girls who are born small for gestational age (SGA) and who could present with an increased risk of early adrenarche, early menarche, and therefore, a premature detention of growth leading to decreased FH.

GONADOTROPIN-RELEASING HORMONE ANALOGUES

During puberty, both growth velocity and epiphyseal fusion accelerate, leading to the completion of most of the long bone growth. Anomalies in the tempo of puberty may influence the FH of affected subjects, so that an early exposure to sexual steroids, as seen in precocious puberty or congenital adrenal hyperplasia, may lead to a reduction in FH, whereas gonadotropin deficiency or estrogen deficiency or insensitivity may be associated with prolonged lineal growth and an increase in FH.

GnRHa administration has been effective in suppressing gonadotropin and gonadal steroid secretion, resulting in slower bone maturation, delayed bone fusion, and an increased FH of some children with gonadotropin-dependent precocious puberty [1–5]. Whether a similar effect can be obtained in short children with either a normal timed or an early puberty (EP) remains to be seen. Initial French studies by Lindner and colleagues [6], Carel and colleagues [7], and Bouvattier and collaborators [8] demonstrated how the parenteral administration of the GnRHa triptorelin, at a dose of 3.75 mg per month, transiently delayed sexual maturation, decreased growth velocity, and retarded bone fusion. However, its effect on FH remained controversial, as both treated and untreated subjects were found to be comparable in terms of adult height. On the other hand, Municchi and colleagues [9] treated children with short stature and normally timed puberty for a period of 4 years, demonstrating an