

Benefit of postponing normal puberty for improving final height

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Abstract

Experiments of nature and clinical observations have provided indications that postponing puberty may increase final height in short children. In children with central precocious puberty, a GnRH analog (GnRHa) alone is efficacious in increasing final height, but in other conditions a combination of growth hormone (GH) and GnRHa is needed. In GH-deficient children with early onset of puberty and poor height prediction, the combination of GH and GnRHa increases final height by 1.0–1.3 s.d. In children with idiopathic short stature and persistent short stature after intrauterine growth retardation, the combination also appears to be beneficial. Potential side effects include weight gain, a negative effect on bone mineralization, and psychosocial consequences. More data on long-term safety have to be collected before the combination of GH and GnRHa in children with idiopathic short stature should be considered for clinical use outside clinical trials.

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Introduction

Growth hormone (GH) therapy is efficacious in increasing growth velocity and final height in children with GH deficiency (GHD), Turner syndrome, renal failure, Prader–Willi syndrome, and idiopathic short stature (ISS) (for review, see Wit (1)). For several other conditions, only short-term efficacy has been shown.

The effect of GH on final height can be influenced negatively by the rapid bone maturation that is seen in puberty. Therefore, there is increasing interest in the role of postponing puberty as a component of growth-promoting therapy (reviewed by Walvoord & Pescovitz (2) and Lee (3)). This form of therapy is aimed at extending the period in which the adolescent can continue growing and thereby increase final height.

In this mini-review, three topics will be discussed: 1) theoretical and observational arguments; 2) experimental evidence; and 3) possible disadvantages of postponing puberty with respect to final height.

Theoretical and observational arguments that postponing puberty may increase final height

In puberty, growth velocity approximately doubles (the growth spurt), followed by a rapidly decelerating growth and ultimately fusion of the growth plates. As males with estrogen-receptor insufficiency (4) or aromatase deficiency (5, 6) neither exhibit a growth

spurt nor close their epiphyses, estrogen in both sexes is the main player in both processes. Part of the estrogen effect may be derived from intracellular conversion from androgens (7), a process called ‘intracrinology’, but androgens may also have a direct effect (8).

Clinical observations of another kind have provided indirect evidence leading to similar conclusions. Firstly, precocious puberty decreases final height, particularly in girls, while untreated hypogonadism leads to tall stature. The timing of puberty has a different effect on the trunk and the long bones: precocious puberty leads to short legs, and hypogonadism to eunuchoid proportions. Moreover, within the normal range, late developers have a greater leg length:sitting height ratio than early developers (9). Secondly, studies on the effect of GH on the growth of GHD children have indicated that children with associated hypogonadism grow taller than children with isolated GHD (10, 11). GH treatment itself may increase the tempo of puberty in GHD children (12) and in children with ISS (13), thereby limiting the effect on adult height.

Therefore, a drug that inhibits puberty, or selectively inhibits the formation or action of estrogen, could be a useful adjuvant therapy in conditions characterized by short stature at the onset of puberty, particularly if puberty should start (relatively) early. This would theoretically lead to an increase of total height gain during puberty. In this review, clinical trials on the effect of a gonadotropin-releasing hormone (GnRH) analog (GnRHa), alone or in combination with GH, on growth, bone maturation and final height in several conditions will be discussed.

Experimental evidence of the effect of postponing puberty on final height

GnRHa alone

The effect of GnRHa in children with early-onset (<6 years) central precocious puberty (CPP) is well documented (see, for example, Klein *et al.* (14)). In most of these children, final height approaches target height. In girls with pubertal onset at 6–8 years, some extra height may also be gained, if puberty is progressing rapidly, bone age is markedly advanced and the predicted adult height (PAH) is low (15, 16). In children with ISS without precocious puberty, the effect of GnRHa alone appears to be limited to 0–4 cm (17–19). In GH-deficient children, GnRHa therapy alone fails to improve height (20).

GnRHa in combination with GH in children with central precocious puberty, congenital adrenal hyperplasia or chronic primary hypothyroidism

In many patients with CPP, timely treatment with GnRHa results in attainment of normal adult height, but some patients do not achieve this. The last of a series of reports from an Italian study (21) has shown that growth velocity and final height are improved by combination therapy. In children with congenital adrenal hyperplasia, the effect of GH or a combination of GH and GnRHa (22) for 2 years resulted in a higher predicted adult height. In children with hypothyroidism, GnRHa or a combination of GH and GnRHa has been tried only in individual cases (23).

GnRHa in combination with GH in GHD

Some children with GHD also have CPP. This is primarily seen in children successfully treated for malignancies, particularly acute lymphoblastic leukemia, by radiation and chemotherapy (24). In these cases, the diagnosis of GHD is easily overlooked, because growth rate may stay normal for a while, as the effect of sex steroids compensates for the growth-retarding effect of GHD. The combination of GH and GnRHa improves PAH (25, 26) and observed adult height (27, 28).

In GHD children with a normal age at onset of puberty who have a low PAH, several studies have been performed on the effect of adding GnRHa to GH therapy. In a prospective, randomized study (29), GH plus GnRHa led to a near final height s.d.-score (SDS) of -1.3 ± 0.5 compared with -2.7 ± 0.3 in the group treated with GH alone. However, there are several methodological issues, namely, that final height was poorly defined, that the patients had been untreated up to the age of 12–18.5 years, and that in several cases growth retardation was less severe than would be expected for untreated GHD patients (30). In two prospective studies (31, 32), the effect of the

combination therapy on final height was 1.0–1.3 SDS. Several uncontrolled studies have indicated a similar positive effect (e.g. 28, 33, 34).

We performed a patient series study with matched controls (30), in which the children were considerably younger and shorter than those in the randomized, controlled trial (29). The effect of GnRHa addition on final height was 1 s.d. (6–7 cm), and final height was close to target height. In a similar study design (35), combined therapy did not significantly increase final height relative to GH alone, but the mean duration of treatment was only 17 months. In this, and another study (28), girls seemed to respond better to the combined therapy than boys. GHD patients with a history of intrauterine growth retardation (IUGR) might benefit more from the combined therapy than patients with normal birth length or weight.

GnRHa in combination with GH in ISS or intrauterine growth retardation

In children with ISS and in patients born small for gestational age (SGA) (also indicated as IUGR), GH is efficacious in increasing growth velocity before the onset of puberty, and when given in a pharmacologic dosage it increases final height in ISS (36) and IUGR (37). However, GH may stimulate a rapid progression through puberty that is expected to reduce final height gain (13). Therefore, the effect of GH might be improved by adding GnRHa.

We carried out a randomized, controlled trial to assess the effect of 3 years' therapy of GH and GnRHa versus no treatment in 36 children with ISS or IUGR (38). At discontinuation of treatment, the estimated effect on PAH was 8.0 cm in girls and 10.4 cm in boys, and the ratio of sitting height to standing height decreased significantly. Final height results will become available soon.

A prospective study to compare the effect of GH alone or GH plus GnRHa in girls with ISS and a relatively early puberty indicated that both regimens increased PAH, but the combination therapy appeared to be more effective (39). Other (uncontrolled) studies on the effect of the combination therapy (e.g. 34, 40–42) reported a gain in final height prediction of between -0.5 and 10 cm. A similar effect was seen in two randomized studies in short adopted girls with early puberty, in which GnRHa plus GH was compared with GnRHa alone (43, 44). After 2 and 3 years, the mean PAH in the combination groups were 2.7 and 4.5 cm greater respectively.

The accumulated evidence shows that the duration of the treatment period is important for the effect on final height. The study by Balducci *et al.* (40) showed a gain in PAH after 2 years of 4.4 cm, whereas the mean completed height was only 1.4 cm greater than the PAH. In contrast, the study by Pasquino *et al.* (39) used a mean treatment period of 4.6 years, and reported a PAH gain of 10.5 cm, of which only 0.5 cm

was lost when the girls were followed to completion of growth (45).

Aromatase inhibitors (ISS males)

Another way to diminish the availability of estrogen is to administer aromatase inhibitors or antiestrogens. The availability of a new generation of potent aromatase inhibitors has allowed their use as a selective tool to delay skeletal maturation without suppressing sex steroids in males, thereby increasing final height. So far, only the short-term results have been reported of the randomized, controlled study carried out in Finland (46). PAH increased after 1 year of treatment, but the serum testosterone levels were extremely high. Final height results are still awaited, and more data on long-term safety have to be collected before its clinical use can be considered (3, 47).

Possible disadvantages of postponing puberty

The differential effect on body segments (towards longer legs) does usually not lead to abnormal proportions, and the effect of GnRHa on becoming overweight is usually modest. Young adults who had been treated with a GnRHa for CPP have normal bone density, but one study has documented a negative effect on bone mineralization for GnRHa-treated short adults (19). A report on GH plus GnRHa in GHD has shown that this may be a temporary effect (48).

The effect of postponing puberty on quality of life is not yet completely clear. In general, a late timing of physical puberty relative to peers has been associated with feelings of being different, which may lead to anxiety and problems in self-esteem, identity and body image (49).

We carried out an extensive psychological assessment before and during the combination therapy with GH and GnRHa in comparison to untreated controls ((38) and H Visser-van Balen, R Geenen, M Moerbeel, R Stroop, GA Kamp, J Huisman & JM Wit, unpublished observations). Before the onset of the study, the results of the questionnaires and interviews with the adolescents themselves did not show any differences from the norm population. The report from the parents, however, described the subjects as showing more withdrawn behaviour, anxiety, depression, social problems and attention problems than the norm group. In addition, the parents mentioned height-related stressors, such as being bullied and juvenilized. Furthermore, 40% of the parents indicated that they worried about the future of their children, in terms of getting a good job and finding a partner.

During the 3 years of treatment (H Visser-van Balen, R Geenen, M Moerbeel, R Stroop, GA Kamp, J Huisman & JM Wit, unpublished observations), adolescents' self-reports showed that both experimental and control groups reported improvement of perceived current height, perceived competence on physical appearance,

and recalcitrance. The control group improved with respect to perceived competence of scholastic ability, athletic ability, inadequacy and trait anxiety, while in the treated group little change occurred. The parents did not report significant changes in their children during treatment. Major psychosocial problems were not found.

Another study dealt with the psychosocial effects of combined GH and GnRHa treatment in adopted children with early puberty (44). Psychosocial problems were not encountered before treatment, and there was no increase of emotional or behavioral problems during treatment. Self-perception did not change, but acceptance by peers increased. It was concluded that delaying puberty by administering GnRHa had no negative effects on psychosocial well-being.

While in GHD patients with a low PAH at onset of puberty, addition of GnRHa appears to be efficacious and safe, in ISS and IUGR it is still open to discussion whether the eventual height benefits of the combination of GH and GnRHa are large enough to compensate for possible adverse effects (on bone mineralization and quality of life). Therefore, this treatment cannot be generally advised. If this combination is considered in individual cases, the adolescent and parents should be well informed that during treatment there is no increased growth velocity, and that the therapeutic strategy aims only at improving final height. It has been speculated that 'many children and their parents will be unwilling to wait so long to reap the benefits of combined therapy' (45), but in our experience adolescents and their parents are usually able to make a rational decision on this matter, and weigh the (partially uncertain) short-term and long-term arguments, including the psychosocial aspects. In the decision-making process, besides the medical aspects, also economic aspects should be considered. For a treatment schedule as used in our randomized, controlled trial, it was calculated that the total cost would be \$105 000 for 3 years (45).

Conclusion

In GHD children who enter puberty when they are short and/or have a low PAH, the addition of GnRHa for approximately 3 years can considerably improve final height. In children with ISS or IUGR who enter puberty relatively early, present data suggest that GH plus GnRHa causes a final height gain of approximately 7 cm. The impact of the treatment on bone mineralization and quality of life is still insufficiently known. Therefore, this treatment cannot yet be generally advised.

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