

## Making Sense of Growth Hormone Therapy for Normal Short Children

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The advent of recombinant growth hormone 20 years ago, which led to increased, albeit expensive, supplies of growth hormone (GH) in the market, has resulted in new treatments for short children. Apart from the 3 traditional indications to improve stature, namely (1) children with growth hormone deficiency, (2) Turner syndrome and (3) chronic renal failure, additional indications approved by the US Food and Drug Administration include children who are born small for gestational age, Prader Willi syndrome, and children with idiopathic short stature (ISS).

Idiopathic short stature (ISS) refers to children who are very short compared to their peers, for unknown or hereditary reasons. ISS occurs in an individual whose height is below 2.25 SD (<1.2 percentile), and it is characterised by normal size for gestational age at birth, normal body proportions, with no evidence of chronic disease or endocrine deficiency, and a growth velocity which is slow or normal. Children with ISS clearly constitute a heterogeneous group encompassing children with genetic or familial short stature and constitutional growth delay (late developers). These children represent the largest population of potential candidates for GH and, incidentally, the largest market for GH. Indeed, market forces which expand the use of GH beyond non-traditional uses have influenced the definition of normality, and have raised the controversy of what is considered treatment, as opposed to cosmetic enhancement.

In the past decade, there have been many studies reporting the use of GH therapy in ISS. However, the efficacy was unclear, as interpretation was hampered by studies involving small numbers of participants, variation in outcome measures, and different and sometimes conflicting results. In addition, ethical and practical issues such as administering long-term injections of placebo to children have affected the performance of the gold standard randomised control trial (RCT). To date, the 5 best quality studies include the following:

1. A meta-analysis by Finkelstein et al<sup>1</sup> examined the effect of GH therapy on short- and long-term growth in ISS. In the controlled studies, the 1-year height velocity of the GH-treated group significantly exceeded controls by 2.86 cm per year. With regard to long-term growth, in 4 controlled trials, the adult height of GH-treated group significantly exceeded controls by 0.84 SD, and all studies suggested an estimated average gain of 4 to 6 cm.
2. The Cochrane systematic review by Bryant et al<sup>2</sup> was a detailed systematic review using a search strategy for RCTs, of which only 9 were found. Quality assessment of trials was performed, based on the Jadad scale to minimise selection, detection and attrition bias, and only 1 trial was of moderate quality, with 8 of poor quality. The Cochrane review concluded that GH improved growth in children with ISS in the short term, with the height SD scores (Ht SDS) ranging from 0 to +0.7 SDS. Despite GH, heights remained relatively short when compared to peers of normal stature, with the majority still at -2 SD. In addition, GH improved final height with limited evidence. There was only 1 RCT reporting final height, and the near final height was 7.5 cm greater with GH. Children in the GH-treated group reported no significant improvement in quality of life issues.
3. Leschek et al<sup>3</sup> performed a double-blind placebo controlled RCT to examine the effect of GH treatment on adult height in peri-pubertal children with ISS. They started with 71 children, but data was eventually available in 33 only. After a mean duration of 4.4 years of treatment, there was a statistically significant, albeit modest, effect of GH on adult heights of children with ISS, with an increase in adult height of 3.7 cm in GH-treated versus placebo-treated subjects. The bone age did not advance significantly during treatment, and did not compromise final height.
4. In the same study, Ross et al<sup>4</sup> reported the psychological adaptation in these children. This aspect of the trial had 68 children participating, using 3 standard tests to measure psychological adaptation. The study found that baseline behaviour, emotional adjustment and self-concept scores for ISS children were within the normal range, and concluded that children with ISS did not

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have problems in psychological adaptation or self-concept.

5. Wit et al<sup>5</sup> recently demonstrated a dose-dependent effect, with a statistically significant difference in the growth response of 2 GH dosages (0.24 vs 0.37 mg/kg/week), with mean overall height gains over the baseline predicted adult heights of 5.4 and 7.2 cm, respectively. Although this difference in adult height was less than 2.0 cm, 94% of subjects receiving high-dose GH achieved adult heights within the normal range.

Based on the evidence to date, GH does improve the physical growth of children with ISS by a modest 4 to 6 cm only, which means that the children are often still short after treatment. However, the fact that ISS can be treated does not necessarily imply that it should be treated. Since the effects are marginal, the rationale for GH treatment in children with ISS should be critically re-examined, with regard to the following issues.

Most children with ISS have no defects in GH secretion or action. The term “idiopathic” is unfortunate, since it implies pathology. However, short stature is not necessarily due to pathology. In any normal population, there will be short normal children who will be at the lower segment of the Gaussian distribution. Without disease, it is hard to justify a rationale for defining a cut-off point for treatment. Indeed, treating short, normal children with GH opens up a Pandora’s box, since it would artificially create a continuing cycle of children falling into the bottom percentile, and thus a new population would be potentially eligible for treatment. In this peculiar situation, treatment of one group creates illness in another group.

More importantly, one must consider whether the modest height gain in ISS from GH treatment is clinically relevant, and whether it translates into any psychological benefit. Society often views short stature as a social prejudice, and assumes that short children will encounter discrimination, which will constitute a psychological disability. However, contrary to expectations, the psychological studies to date have not shown that short children have problems in psychological adaptation.<sup>4,6</sup> While the children may have reported teasing and being treated as younger than their age, these stresses may not necessarily translate into psychological maladjustment. Further studies should be made to determine if the added height with GH is really worth anything to the treated children, and to exclude a placebo effect.

If the children have not been shown to have clear psychological benefits from the modest increment in height, are we then treating the parents – parents who may have a complex that their short child is disadvantaged, or parents who demand GH for their children to help them grow taller? Furthermore, once GH is commenced, the problem

of how much to use, and when to start or stop arises, because the aim of treatment may be distorted with time, from attempting to achieve “normal” height to aiming for “maximal” height. Unfortunately, the clinical limits for treatment for ISS have not been clearly defined yet.

Considering the child who has to receive nightly injections of GH, treatment may cause the child to assume that being short is a disease. By administering GH, the unhealthy message may be reinforced that children should change physically to accommodate societal biases. Parents are often concerned that short stature will lead to discrimination. Since discrimination is a disease of society, societal intolerance may be better addressed by re-educating the public and counselling the family, rather than by administering GH to the short, normal child. In the long term, it may be better to teach coping mechanisms, an important life lesson to deal with adversity, rather than to resolve adversity through medication.

There are also concerns regarding the long-term adverse effects of GH which are largely unknown, as the children have not been followed up long enough. To date, GH has been relatively safe, with no significant adverse effects reported. However, further studies are important to assess the association of long-term GH and the risk of malignancy, especially in those who may be genetically predisposed.

Lastly, there is a considerable financial burden to the family and society with the use of GH. The estimated cost is US\$20,000 (~S\$33,000) per year for treatment. For a 30-kg child, the estimate may be as high as S\$23,000 per 1-cm increment in height. Is this cost-benefit assessment meaningful? This raises another interesting ethical issue that normal children who can afford GH will grow taller, and those who cannot afford it will remain relatively shorter.

In the final analysis, the medical decision to use GH for ISS is controversial and individual. If it is used, the doctor should:

- a. provide realistic evidence on expectations in final height;
- b. emphasise that there is no current evidence that GH improves the quality of life;
- c. discuss the potential for side effects, that long-term side effects are not known;
- d. disclose that the cost is substantial;
- e. monitor closely for complications.

However, it is important to re-emphasise that ISS is a heterogeneous group and a diagnosis of exclusion. Although the majority of children are normal, some children with ISS may well have subtle abnormalities of GH secretion and response, and will benefit from GH. Anecdotally, these children would be those with poor height velocities (at or below 4 cm per year), low or elevated IGF-1 levels, and

often demonstrate a striking increase in height velocity (up to 4 cm) within the first 6 months of treatment. The main challenge lies in identifying these children. As research continues into the molecular basis for the heterogeneous conditions that constitute ISS,<sup>7</sup> it is likely that future optimisation of cost-benefit ratios for GH therapy in ISS will be improved.

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