

## Controversy

# Which children should receive growth hormone treatment

### Reserve it for the GH deficient

Growth hormone (GH) has been in clinical use for four decades and there has been much rediscovery of wheels in the past 30 years.<sup>1</sup> Childhood growth is GH dependent. Velocity is related to the amplitude of pulsatile GH secretion in an asymptotic manner so that children with very little GH grow very slowly and a small replacement dose has a large effect on growth acceleration. The more GH a child secretes, the more normally he or she grows, the bigger is the dose of GH needed to have a significant effect, but any child given GH in adequate amounts grows more quickly.<sup>2</sup>

To maintain peak concentrations of GH, the pituitary has to increase production as the child grows. This may not happen in some children who then grow poorly in the middle childhood years. When growth is complete and the demand for GH drops, they have ample GH for adult life, which is why most patients do not continue to require treatment. Lack of puberty may give rise to another transient GH insufficient state.

The indication for GH replacement is GH deficiency, congenital or acquired, permanent or transient. GH should be introduced as soon as the failure of its secretion has been identified. The dose is dictated by the clinical situation but there is a tendency to maximise doses at the start of treatment in order to restore lost growth in the least time, with probable long term benefit.<sup>3</sup>

Normal children, children with Turner's syndrome, renal failure, skeletal dysplasia, etc, all grow more quickly when given GH, but results on adult heights are not all that exciting. This is not surprising as none of the children are GH deficient and GH does nothing for the severity of their underlying conditions. In 50% of patients, predicted height is improved by 5–10 cm. Is this useful?

Short children or adults carry no quantifiable disadvantage and their stature should not be used as an explanation for bullying or being bullied at school, or for losing out in later life.<sup>4,5</sup> Treatment confers a label and a label carries a stigma. It is important not to stigmatise short people but to accommodate the disadvantage they may perceive and (possibly) help them come to terms with it. The cost of treating two children with GH for one year would buy a clinical psychologist for a year from which more than two patients might well benefit. Children growing at a normal growth velocity should not be treated, regardless of their height.

GH side effects in children have been few, but GH has much of its effect through the generation of insulin like growth factors and insulin itself, and all treated children are in a state of (reversible) hyperinsulinaemic euglycaemia. GH causes water retention,<sup>6</sup> and although treated children rarely become hypertensive, their blood pressure might be higher than it might have been. As GH has a major lipolytic action, the atherogenic soup which GH induces needs to be remembered. There is an association between acromegaly and cancer,<sup>7</sup> although extensive studies have not revealed an increased incidence of leukaemia nor relapse from brain tumours in treated children.

I would be chary of encouraging anybody to have hormone replacement if they were not deficient of that hormone. GH is no different. It is negligent not to replace hormones when they are deficient.

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### Cost-benefit analysis is the key

Growth hormone (GH) therapy for clearly growth hormone deficient short children is well accepted. Treatment of those with no recognisable abnormalities in their GH–insulin like growth factor I (IGF-I) axis—idiopathic short stature (ISS)—remains controversial. However defining GH deficiency (GHD) is arbitrary owing to poor efficiency, sensitivity, and specificity of GH stimulation tests.<sup>1,2</sup> Many patients labelled as having idiopathic GHD, treated successfully with GH, would be better categorised as ISS. Likewise, many currently diagnosed as GH deficient from GH stimulation tests may have normal spontaneous GH secretion and IGF-I concentrations and should be diagnosed as ISS.<sup>3,4</sup> Some children may have high GH concentrations but remain short because of GH insensitivity. We remain poor at predicting response and evaluating appropriate end points for treatment efficacy—final height, short term catch up growth, quality of life, metabolic parameters—both in classical GH deficiency and in other disorders where GH therapy seems “effective”, such as Turner syndrome or chronic renal failure.<sup>5</sup>

“Normal” means physiologically correct, not “average”, “common”, or “conventional”.<sup>6</sup> The World Health Organisation defines health as not merely absence of disease, but a complete state of mental, physical, and social wellbeing. Moral objections to growth promoting treatment may be based on the view that the aim of treatment is to enhance normal physical characteristics.

A crucial purpose in increasing adult height (if achievable) is resulting psychological or quality of life gain.<sup>6,7</sup> Once confounding factors (for example, socioeconomic level) have been excluded, children with short stature have not been shown, as a group, to display clinically

significant behavioural or emotional problems.<sup>8–10</sup> On an individual basis, however, short stature may be the additional stressor which leads to psychological maladaptation. In the context of other treatments for conditions not related to disease or dysfunctional states, treatment of short children without “GH deficiency” to normalise conventionally defined abnormally short stature should be seen as ethically acceptable.

GH therapy must also be seen in a broad context: in individuals born small for gestational age, catch up growth is not necessarily achieved without adverse metabolic consequences—those who remain short as adults may have more favourable cardiovascular risk profiles. Thus cost–benefit analysis is key to GH prescribing decisions in any diagnostic context and requires detailed knowledge of physical (improved height, absence of side effects<sup>11</sup>), psychosocial, and quality of life outcomes. Values ascribed by an individual child to potential outcomes should be central to an age appropriate discussion process. In this respect, models enabling individualisation of prediction are promising, will also highlight deviation from optimal responses, and help with understanding pathophysiology.<sup>12</sup>

Currently, evidence for GH efficacy is frequently lacking or biased because of badly designed studies of too few patients.<sup>3 5 13</sup> Future national or international prospective, randomised, controlled studies should not compare outcomes with poorly predictive surrogate markers (predicted adult height, target height) and must incorporate intention to treat analysis of “drop outs”. Prescribing decisions must be based on systematic evidence review and explicit linkage between recommendations and graded evidence levels.<sup>14</sup> Statistically significant effects (for example, increased final height) must be evaluated in terms of clinical benefit—alleviation of short stature related suffering is crucial.<sup>15</sup>

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## Long term side effects possible with high doses

The exciting thing about the administration of growth hormone (GH) is that it initially makes almost all children grow faster with the expectation of an appreciable increase in adult height. Today it is estimated that some 4000 children are receiving this treatment in the United Kingdom at an annual cost of £25m.

Although growth hormone deficiency, Turner syndrome, and chronic renal failure are the three licensed indications for treatment of children in the United Kingdom, studies also include children with idiopathic short stature, intrauterine growth retardation, Prader-Willi syndrome, Noonan syndrome, skeletal dysplasias, and others. The use of GH in these conditions has been the subject of two excellent recent reviews.<sup>1 2</sup>

Data are now available on the increase in final height achieved, but unfortunately these have often been disappointing outside severe GH deficiency.<sup>1–3</sup> There are also special problems for some groups, such as those who have received craniospinal irradiation or have early puberty or a skeletal dysplasia where growth potential is naturally reduced and appreciable gain less likely. Although the benefits of treatment must be judged on height gain or changes in body composition sufficient to improve quality of life, this information is sadly lacking from control trials. How much additional height is needed to justify injections of GH in a child for a 10 year period? Thirty four Canadian paediatric endocrinologists advised a median of 5 cm with a range of 4–10 cm in girls with Turner syndrome (D Stephure, personal communication, 2000), but is this increase appropriate justification? Further data are needed on what the children and their families believe to be beneficial.

All reports show a wide range of response to treatment, with some children growing more than others, and the next challenge is to identify positive predictive factors. As final height data become available with varied treatment regimens, the need for randomised control trials becomes even more obvious. Where expected gain is only minimal, should treatment be started or even stopped if the initial increase is below set guidelines?

GH has now been available for four decades, and the newer biosynthetic preparation has been used for the last 15 years with a remarkably good safety record.<sup>4</sup> However, as investigators seek further height gains in non-endocrine short stature by using larger and larger doses above that used for GH deficiency, then the potential for long term complications increases.<sup>5</sup>

GH treatment induces insulin resistance, and a recent publication indicated a sixfold increase in type 2 diabetes that did not resolve when treatment was stopped.<sup>6</sup> The authors highlighted the importance of long term follow up of treated children particularly at risk of type 2 diabetes, such as those with obesity, Turner syndrome, intrauterine growth retardation, Prader-Willi syndrome, and GH deficiency secondary to other causes. Although further data are still required, this report highlights the importance of collecting reliable long term surveillance data.<sup>7</sup>

GH treatment has undoubtedly made many children with severe GH deficiency taller adults over the last 40 years. However, in deciding who should receive treatment outside this indication, doctors, parents, and children must be fully informed of the current expectations of height gain outside the individual impressive report.<sup>5</sup> They should also be aware that at present there is no evidence of improvement in the quality of life and that there may yet be long term significant side effects, particularly when high doses are prescribed.

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