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Dawn R. Bucher  
*Columbia University, NY*

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## **Ethical Considerations: Growth Hormone Treatment in Children with Idiopathic Short Stature**

**Dawn R. Bucher**  
Columbia University, NY

### **Abstract**

**Being short is a natural diversity of the human race. In 2003, the Food and Drug Administration (FDA) approved the use of growth hormone (GH) for the treatment of idiopathic short stature (ISS) in children. Research has shown that GH therapy in children with ISS has a variable effect on increasing height. However, the literature has not shown the efficacy in improving psychosocial function to justify the costs and potential adverse effects. GH use in children with ISS is a subject of great ethical debate. Ethical implications including beneficence, nonmaleficence, autonomy, and justice are discussed. ISS requires thoughtful consideration by the patient, parents, and healthcare professionals. Well-designed long-term studies are needed to determine the benefits of such treatment.**

**Keywords: Idiopathic Short Stature; Growth Hormone Therapy; Ethics; Children; Healthcare Professionals**

## **Ethical Considerations: Growth Hormone Treatment in Children with Idiopathic Short Stature**

### **INTRODUCTION**

Being short is a condition for millions. In the United States, there are an estimated 1,062,000 children with Idiopathic Short Stature (ISS) and 24,000 with medically defined short stature between the ages of 4 and 15 years (Holden, 2000). Not all children with short stature seek hormone treatment. In Minnesota, there are approximately 19,000 children ages 4-15 years with ISS (Holden, 2000). However, based on Genentech reports, only 55 children are receiving growth hormone therapy (Holden, 2000).

Being short is part of the natural diversity of the human race. However, some short people and parents believe shortness is a disability. Numerous reports in the scientific literature state short people, especially males, are stigmatized, have low self-esteem, less academic achievement, lower income and social status (Allen & Frost, 1990; Cuttler, 2004; Willhaus, 1999). Some are teased and bullied as children, causing psychological distress (Allen & Frost, 1990; Cuttler, 2004; Willhaus, 1999). Other reports indicate that short people may have some advantages over tall or average height people. For example, they have faster reaction times, stronger muscles, and greater endurance (Samaras, nd). They are less likely to break bones after a fall, and less likely to require surgery for herniated spinal disks (Samaras, nd). Short people do well in sporting events such as gymnastics and wrestling. Willhaus (1999) reports there are no actual differences in intellectual function, academic achievement, visual-motor intelligence, or psychosocial adaptation between short children and tall to average children.

Over the past 40 years, more attention has focused on the causes of short stature. Certain diseases such as growth hormone deficiency, Turner's syndrome, chronic renal insufficiency and Prader-Willi syndrome inhibits growth in children. The development and approval of

biosynthetic growth hormone (GH) in 1985 has improved growth retardation in children (Cuttler, 2004). Most recently, July 2003; the FDA approved the use of GH for the treatment of ISS in children, a condition that has no known cause.

ISS is defined as short stature in an otherwise healthy child, exclusion of other causes of short stature, bone age within 2 standard deviations (SD) of chronological age, a height below the 3<sup>rd</sup> percentile for that age and sex in the same ethnic group, or normal growth hormone response on provocative testing (Lee, 2006; Manmohan, 2005). FDA indications for growth hormone therapy in children with ISS include no diagnosis of growth hormone deficiency, height that is more than 2.25 SD below the mean for sex and age, open epiphyses, and growth rate that is unlikely to attain an adult height within the normal range (Lee, 2006). The approval of GH therapy in children with normal hormone levels raises many interesting, curious, and thought provoking ethical questions.

### **BENEFACTENCE AND NONMALEFACTENCE**

Beauchamp and Childress (2001) define beneficence as an action done to benefit others, while nonmaleficence is an obligation not to inflict harm on others. If one believes that 4 to 7 cm in height promotes physical functioning and social well-being with no serious side effects then GH therapy may be beneficial. However, no well-designed evidenced based studies have demonstrated that rhGH therapy in ISS children achieve better psychosocial functioning. Nor do studies demonstrate that GH increases final adult height (Brown, 1997). Some studies even found that the gain was only 4-6 cm and that even this result was variable, not consistent (Finkelstein et al., 2002; Hintz et al., 1999; Wit & Rekers-Momberg, 2002). Many medical ethicists are concerned that health care providers will start treating “normal” as a disease

(Caplan, 2003). Even though the child may be below the 3<sup>rd</sup> percentile on the growth chart, he/she may only be on the low side of a scale. They are not considered as having a disease or disability by most standards. Health care providers need to explain this to the child and his/her parents.

Unrealistic expectations and treatment failure can lead to disappointment, clinical depression, and feelings of anger not only in the child, but also in parents (Pilpel et al., 1996). Health care providers need to take this into consideration before initiation of GH therapy. Assessment of the patient's psychological well-being, social stressors, and the family's concerns and expectations are necessary in the treatment of ISS, along with family and medical history, detailed physical exam, and laboratory, imaging, and growth data (Lee et al., 2006). Possibly, an evaluation by a licensed psychologist or specialist in this area should be required to discuss and educate the child and other family members of such treatment and alternatives. Dr. Cupoli recommends and uses psychotherapy to focus on the patient's losses and anger before addressing short stature (Stein et al., 2004). More studies are needed to determine the beneficence and nonmaleficence of growth hormone therapy in children with ISS. Is the child with ISS benefiting in any large degree from the use of growth hormones?

Another issue has to do with the safety of this therapy and the incidence of side effects. GH therapy is considered to be safe, exhibiting minor side effects such as pain, rhinitis, headache, arthralgia, paresthesia, injection site burning or pain, weakness. Some children have developed diabetes-like conditions, renal and metabolic conditions, and antibody production (Holden, 2002; Mitchell, nd.; Physicians Committee for Responsible Medicine, nd). Other studies have shown the incidence of slipped capital femoral epiphysis, carbohydrate metabolism, and neoplasia have been low but these studies were relatively small and of short duration (Kemp

et al., 2005; Quigley et al., 2005). However, the vast majority of patients treated with growth hormone therapy experienced no adverse effects and many of the reported side effects can be controlled (Holden, 2000). There has been no reported mortality associated with GH therapy use in children.

Although GH therapy has been around for decades, the safety and efficacy of long-term use of rhGH in children with ISS (non-GH deficient short stature) is unknown at this time. There are some concerns that long-term administration of growth hormone therapy in supraphysiological doses may lead to malignancy, slipped capital femoral epiphysis, carbohydrate metabolism and irreversible joint disturbances years after treatment therapy (Holden, 2000; Kemp et al., 2005; Quigley et al., 2005). However, there are no current studies specifically linking hormone therapy to these diseases. Nevertheless, surveillance is needed to determine if there are any long-term serious side effects of rhGH therapy in children with ISS. Questions of beneficence and non-maleficence could be raised in regard to definitions of side effects and controlling them with additional interventions.

## **AUTONOMY**

According to the literature, short people have emotional and behavioral problems, low job satisfaction, less marital success, social isolation, and low self-esteem (Sandberg et al., 2004; Willhaus, 1999). However, the literature is not clear about the source of the emotional and behavioral problems suffered by short people. Is their height the cause of these problems, or are other factors responsible? Some short children are teased and perceived as younger than actual age; however, researchers have not found any association with these experiences and psychological dysfunction (Sandberg et al., 2004).

A second ethical consideration relates to autonomy. Beauchamp & Childress (2001) defines autonomy as one's ability to make one's own health care decisions especially pertaining to informed consent and refusal of treatment. One can argue that children often do not have the ability to make their own decisions in medical matters. Does a child, age 6, have the ability or understanding of the consequence of what it means to take GH therapy every day for 3 to 9 years? Do they understand the possible side effects and commitment involved in GH therapy? Autonomy and responsibility in children are difficult to comprehend and measure. Anderson (1993) reports that health care providers chose an average age of 10.3 for making such medical decisions. However, many children involved in GH therapy for ISS are seen in the clinic at a much earlier age. In contrast, if health care providers wait until the child is old enough to assent to GH treatment; the effects of treatment therapy may be too late.

Parents are the legal guardians of their children and are the ones that make the vast majority of child raising decisions. It is also believed that being short is more of a concern with parents than it is with the child. Sandberg and colleagues (2004) detected no significant relationship in height and friendship, popularity, or reputation among peers in grades 6 through 12. They found that social behavior, friendship, and acceptance among peers had a minimal impact on extreme stature. In addition, Ross and colleagues (2004) found no association with problems in psychological adaptation or self-concept in short stature children with ISS. However, they did show an association with improved behaviors in the children with ISS measured by the parents' questionnaire. Thus, health care providers need to carefully assess the need for GH therapy in children with ISS and assess the parents' perception of short stature.

**JUSTICE**

Justice is the fair and equitable distribution of healthcare resources (Cook et al., 2004). The cost of hormone therapy and the long-term commitment to such therapy must be considered. Biosynthetic rhGH therapy is one of the most expensive treatment regimens available. For a child weighing 30kg, using traditional dosing guidelines, the yearly cost of injections is approximately \$15,000 to \$20,000 (Allen, 2006). This cost does not include office visits or higher doses of rhGH. The cost per inch (2.5 cm) of adult height growth is estimated to be \$35,000 to \$52,000 (Finkelstein et al., 2002; Freemark, 2004; Lee et al., 2006).

Children with ISS require rhGH injections for several years. On average, 3 to 9 years is required for the treatment of ISS (Willhaus, 1999). Studies have also showed that daily rhGH injections are more efficacious than three times per week. However, one study showed a high attrition rate for patients using a long-term regimen of daily injections (Leschek et al., 2004), while another study showed high attrition rate with injections three times a week (Ross et al., 2004). Noncompliance and interruption of therapy can compromise expected gains in height and result in treatment failures (Lampit & Hochberg, 2002).

The American health care systems excludes >45 million people from any health insurance (Allen, 2006). How does one prioritize rhGH therapy? Strategies are needed to decrease the cost of such therapy. More studies are needed to determine a consistent treatment regimen for children with ISS. Either treating earlier in childhood or seizing treatment at a “normal” rather than “maximum” height should be a goal (Allen, 2006). Many questions and concerns arise regarding the equitable distribution of health care resources and the economic effect on the health care system. Do the benefits of the current intervention justify the cost of a condition that is referred to as “normal-variant short stature” with an unknown cause?



**RECOMMENDATIONS**

Parents, children, and healthcare providers may need to find other ways to deal with the physical and psychological implications of ISS. The stigma of short stature can be addressed in a number of ways. Parents, teachers, nurses, nurse practitioners, other health care providers, and society can be influential by interacting with the child according to their age and intellect, not their height. They can help by interceding in conflicts where teasing and name calling by other students are directed at short people. They can encourage short stature children to participate in sports and activities that do not require one to be a certain height to participate. Role modeling, promoting positive self-image and self-worth, and developing a supportive, nurturing home and school environment all can improve the child's self-confidence. In addition, parents of children with ISS may need to undergo counseling and receive education about the limitations of rhGH therapy.

More well-designed long-term studies are needed to determine the safety and efficacy of rhGH therapy. Also, it will be imperative to conduct a survey on the parents and children who have used growth hormone therapy in the past to determine if the treatment and effects are worthwhile.

**CONCLUSION**

Growth hormone therapy in children with ISS is a subject of great ethical debate. The benefits of GH therapy in children may or may not provide the means to overcome the physical or psychological impact of being short. The current research studies show individual variability in growth response. Not all children achieve their adult height above base-line predicted height. Do these small gains in height impact the child adequately to justify the expense, time, or

psychological benefits of such therapy? As healthcare providers, we can help educate parents, children, and teachers in helping the child with ISS improve quality of life by other means.

Long-term evidence based studies are needed to determine the benefits of such treatment.

ISS is one of many elective treatments for a condition that may or may not be damaging to patients. Growth hormone injections for the treatment of ISS require thoughtful consideration by the patient, parents, and medical providers. The efficacy may be marginal though appreciated by some.

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