

When should doctors treat short children and teens with growth hormone?

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When is it appropriate to treat short children with growth hormone? The answer is not always clear-cut, as many parents and physicians have discovered over the past three decades.

Social, medical and ethical concerns complicate the issue. Short stature itself is not a disease, although it may result from underlying disease. But diagnosis can be challenging and treatment decisions may be controversial. Some short but healthy children receive expensive nightly injections of recombinant growth hormone. As with any medicine, there may be side effects—and possibly unknown long-term risks.

A group of medical experts has weighed existing evidence and issued a new set of clinical guidelines for managing children and adolescents with growth failure. Written on behalf of the Pediatric Endocrine Society, the guidelines are the society's first update since 2003. For children with certain clearly diagnosed medical conditions, the experts recommend hormonal treatments. When the cause of growth failure is unknown, they advise against routine growth hormone use and recommend a more measured decision-making approach.

"The nuances of this issue leave much room for open questions and differences of interpretation," said study leader Adda Grimberg, MD, a pediatric endocrinologist at Children's Hospital of Philadelphia (CHOP). "In developing these guidelines, we analyzed not only the results, but the strengths, limitations and potential biases of studies in a large evidence base that continues to evolve."

Grimberg and colleagues issued their guidelines through two committees of the Pediatric Endocrine Society—the Drug and Therapeutics Committee and the Ethics Committee. The guidelines appeared online Nov. 25 in *Hormone Research in Paediatrics*, and in the January 2017 print issue.

The co-authors included seven pediatric endocrinologists from different centers in the U.S. and Canada, plus a pediatric bioethicist and a consultant for the group's methodological approach. Using that method, called GRADE (Grading of Recommendations, Assessment, Development and Evaluation), the co-authors generated a series of strong recommendations, conditional recommendations and ungraded good practice statements.

The authors focused on three diagnoses: growth hormone deficiency (GHD), primary IGF-I deficiency (PIGFD) and idiopathic [short stature](#) (ISS). In GHD, a child does not produce enough growth hormone, and the authors strongly recommend the standard treatment with recombinant growth hormone.

Human growth hormone normally acts along a signaling pathway that stimulates production of IGF-I growth factor, which then affects body tissues such as the growth plates in bones. Therefore, growth hormone deficiency often causes IGF deficiency downstream. However, in PIGFD, a patient has sufficient growth hormone but has a biological defect that reduces the production or action of IGF-I growth factor. Because under-nutrition is a common cause of low IGF-I levels, physicians must first rule out a nutritional problem before diagnosing IGF deficiency. For true PIGFD, the authors endorse treating children with recombinant IGF-I growth factor.

In ISS, the cause of [short stature](#) is unknown. The U.S. Food and Drug Administration has defined ISS as height that is more than 2.25 standard deviations below the mean height for a patient's age and gender, without evidence of underlying disease. This statistical definition corresponds to the shortest 1.2 percent of the U.S. population: adult heights below 5 feet, 3 inches for men, and below 4 feet, 11 inches for women.

For children with ISS, the authors offer a conditional recommendation, advising against routinely using growth hormone treatment. Instead, they recommend that parents and clinicians take a shared decision-making approach, weighing physical and psychological burdens for the child, along with a discussion of risks and benefits.

"Growth hormone treatment for patients with growth hormone deficiency offers health benefits beyond height," said Grimberg, "but growth hormone treatment for ISS is solely about height. Another important difference is that, unlike patients with growth hormone deficiency, not all patients with ISS increase their height in response to growth hormone treatment. So a decision for treating ISS is more of a subjective judgment call than for growth hormone deficiency."

Much of the controversy in growth hormone treatment involves ISS. The authors note that, in practice, families of many children who are short but do not meet the FDA definition for ISS have sought growth hormone treatment to make them taller. Grimberg previously showed in national research that gender bias influences both referral and treatment patterns for short children. Short boys are three times more likely than short girls to be treated with growth hormone for ISS, even though equal proportions of both genders fall under the ISS height threshold. One consequence is that short girls with underlying disease may be overlooked, while short, healthy boys may receive unnecessary treatments.

Moreover, short-term gains in height do not always translate into adult height differences. A full study of long-term results would require many years to complete, and thus is often expensive and unfeasible to perform.

"We found large gaps in our knowledge of growth hormone treatment," said Grimberg. "For instance, we know little about the long-term risks of nightly hormone injections given for years. We don't even really know the relationship between adult height and adult quality of life."

Other research gaps exist in diagnosing growth [hormone deficiency](#). Because diagnostic tests have

evolved over time, different tests can provide different results for the same sample—making it harder to understand the scientific literature over time.

Given the current state of knowledge, there are ethical questions in addition to medical questions surrounding growth hormone treatment for short children who don't have a disease. "Administering growth [hormone treatment](#) may help very short children gain a few inches in height, but it also exposes them to a powerful hormone when we do not fully know the long-term implications," said co-author Chris Feudtner, MD, PhD, a CHOP pediatrician and director of the hospital's Department of Medical Ethics.

While endorsing further research to address the many unanswered questions in the field, the authors recommend that only pediatric endocrinologists manage evaluation and treatment for [growth hormone](#) deficiency, ISS and PIGFD in children. "The rigorous methods were designed to create recommendations at the group level," Grimberg added. "However, due to inter-individual variability, it is important for clinicians to weigh the potential benefits and risks of treatment for each individual patient in the context of the evolving evidence base."

More information: Adda Grimberg et al, Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency, *Hormone Research in Paediatrics* (2016). [DOI: 10.1159/000452150](https://doi.org/10.1159/000452150)

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