

Idiopathic Short Stature



The mission of the Human Growth Foundation is to help children and adults with disorders related to growth or growth hormone through education, research, support and advocacy. The Human Growth Foundation is dedicated to helping better understand the process of growth and the treatment of growth disorders. Its objectives are:

- Support of research
- Family education and service
- Public education
- Education of healthcare professionals

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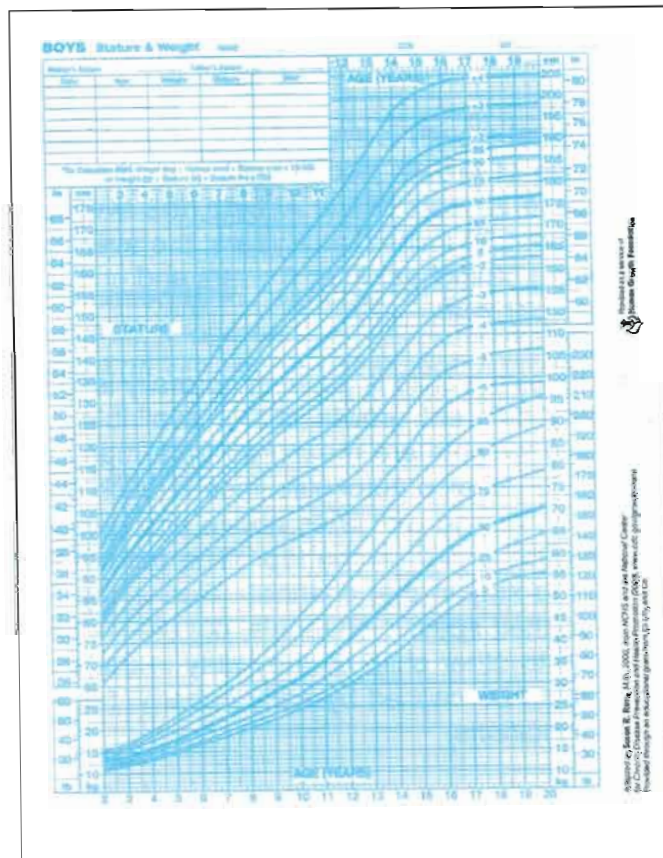
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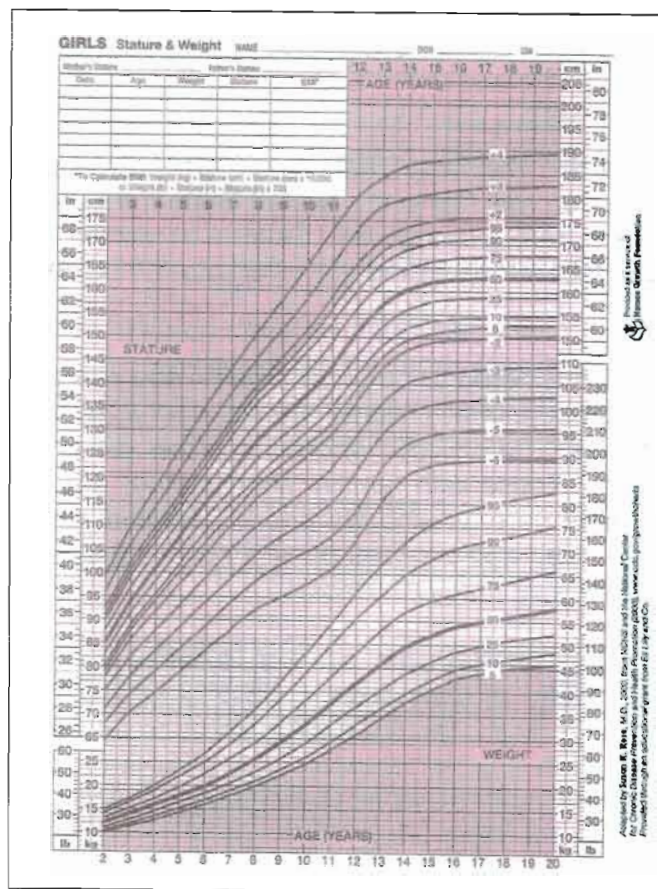
Review of Normal Growth: Normal growth is the result of several factors, such as nutrition, genetics, and hormones. The most rapid phase of growth occurs in the mother's uterus. After birth, the growth rate gradually declines over the first several years of life. At birth, the average length of a newborn is 20 inches; at 1 year, the average height is about 30 inches; at 2 years, the average height is about 35 inches; and, at 3 years, the average height is about 38 inches. After 3 years and until puberty, linear growth continues at a relatively constant rate of 2 inches per year.

Growth Charts: The best way to tell if a child is growing normally is to plot the child's height and weight on a growth chart. There are many different growth charts available. Most are constructed from cross-sectional data; that is, heights and weights are measured from many children at different ages, and then the data are analyzed statistically to develop percentile lines at each age. The result is a growth chart with a heavy central line at the 50th centile and with lines above and below representing various centiles from the 3rd or 5th at the bottom to the 95th or 97th at the top. The pattern that most children follow is to find a channel on the growth chart and to stay in that channel. During the first year or two of life children may cross channels as they settle in to their specific channels, but unless there is acceleration or slowing of the growth velocity (speed) compared to other children they stay in the same place relative to other children. Acceleration of growth velocity could be caused by early puberty, for example. Slowing of the growth velocity could be caused by many conditions.

Male Chart Ages 2 Years to 20 Years



Female Chart Ages 2 Years to 20 Years



- Endocrine Control of Growth:** In order for normal growth to occur several hormones must be in place, in particular, there must be adequate thyroid hormone and growth hormone. Growth can also be slowed if there is inadequate insulin, as in the case of a child with poorly controlled diabetes. Growth will also be slowed if there is an excess of cortisol.
- Other Factors Influencing Growth:** The factor that causes most of the poor growth that is seen worldwide is malnutrition. Although we don't often see this in the United States, we do occasionally see children who have a chronic disease that keeps them from growing well. Several examples of disorders that cause poor growth but may not be apparent without laboratory testing are inflammatory bowel disease (especially Crohn's disease) and renal tubular acidosis.
- Pathologic Growth:** A child is considered to be short if he or she has a height below the 3rd or 5th percentile on a growth chart. Three to five percent of all children are considered to be short. However, many of these children have normal growth velocities. The children who fall into this group include those with familial short stature or constitutional growth delay. Those with familial short stature are born with genes that determine their short height, and they usually have parents who are short. Constitutional growth delay is a term used to describe children who are small for their age but who have a normal growth rate. Of all children with short stature, only a few have a specific treatable medical condition.

Growth failure is a term used to describe a growth rate that is below the appropriate growth velocity (speed) for age. The term growth delay may refer to a situation in which a child is short but appears to be able to grow longer than children usually do, and thus, may not end up short as an adult. Dwarfism is a term that has often been used to describe extreme short stature; however, the term is unflattering and its use is often avoided. Growth hormone deficiency is sometimes called pituitary dwarfism. Short stature may be a normal expression of a person's genetic potential and, therefore, the growth rate is normal. Short stature may also be a result of a condition that causes growth failure and a growth rate that is slower than normal.

Differential Diagnosis of Short Stature or Growth Failure

- **Familial Short Stature:** Children with this condition have parents with short stature. They have a normal growth velocity, and bone age is not delayed. They enter puberty at a normal time and often complete growth with a short adult height.
 - **Constitutional Growth Delay:** Also called delayed puberty, children with constitutional growth delay have a normal birth weight, and their growth slows, usually during the first year of life. From about age 3 to puberty, these children have an adequate growth velocity. Bone age is usually delayed, and puberty is late. Late puberty allows for more prepubertal growth, usually resulting in a normal adult height. Usually, children with constitutional growth delay do not show growth failure, but a period of slow growth velocity occurs during the first year of life and just before puberty.
 - **Malnutrition:** Worldwide, malnutrition is probably the most common cause of growth failure and is usually poverty related. Nutritional deficiencies in developed countries are more often the result of self-restricted diets. Poor weight gain is often more noticeable than short stature.
 - **Diseases and Disorders:** Chronic diseases and systemic disorders that involve the nervous, circulatory, or gastrointestinal system may be a cause of growth failure. Diseases or disorders involving the liver, kidneys, lungs, or connective tissue may also be a cause.
 - **Psychosocial Dwarfism:** This is a disorder of short stature or growth failure and/or delayed puberty. This often occurs in association with emotional deprivation and/or child abuse and neglect.
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- **Syndromes:** Growth failure can be a feature of genetic syndromes, such as Turner syndrome and Down syndrome. It can also be a part of other syndromes, such as Noonan Syndrome, Russell-Silver syndrome, and Prader-Willi syndrome. Endocrine (hormonal): Endocrine causes include thyroid hormone deficiency (hypothyroidism) growth hormone deficiency, or other hormone disorders. Thyroid hormone is necessary for normal growth; in children with hypothyroidism, growth is extremely slow. Children with growth hormone deficiency have normal body proportions, but they may appear younger than their actual age.
 - **Other:** Growth failure may be related to intrauterine growth retardation (a condition in which children weigh less than 5 lbs. at full term or who are small for gestational age if born preterm). Bone and cartilage disorders (called chondrodystrophies) may also be a cause of growth failure. Achondroplasia (one of the most common conditions that causes growth failure and short stature) is a genetic disorder of bone and cartilage. Persons with achondroplasia have a normal-sized trunk, short arms and short legs, and a slightly enlarged head with a prominent forehead. Adults with this condition are typically about 4 feet tall. There are other chondrodystrophies, such as hypochondroplasia, which are similar to achondroplasia, but not as severe.
 - **Height Predictions:** There are a number of ways to predict a child's adult height. The first is to use the height of the child's parents. We simply take the mean (average) of the parents' heights and then (since women are about 5 inches short than men on average) we add 2½ inches if the child is a boy or subtract 2½ if the child is a girl. The actual name for this calculation is the "sex-adjusted mid-parental height," but most people call it the "target height." This height represents the peak of the bell-shaped curve, which is the most probable adult height based on the child's genetic background (i.e., the parents' heights). It is important to remember that there are many people whose heights fall on either side of the bell-shaped curve, so while it is statistically the most probable adult height, there are no guarantees that a particular child will fit this exactly.

Another way of predicting adult height is to use the bone age. Simply plot the child's height on a growth chart using the bone age instead of his or her age. There are tables for using the bone age to make height predictions, known as the Bayley-Pinneau tables. Height prediction has been further refined by including other variables, such as weight and parental heights. In general, all of the methods work, but they work best when comparing groups of children. While it is tempting to believe height predictions, predictions are still guesses, and while they may be useful, they should be looked at cautiously.

Definition of ISS: Idiopathic simply means we don't know. Thus, idiopathic short stature describes a child who is short, and who has been examined in order to try to find a cause for the short stature, but no cause has been found. In particular, the child is not growth hormone deficient and does not have any other known cause for the growth disorder. When the FDA approved growth hormone therapy for idiopathic short stature in 2003, they set several criteria for the definition, which includes 1). not being GH deficient, 2). having a height that is more than 2.25 standard deviations below the mean, 3). having open growth plates on a bone age x-ray, and 4). not having a syndrome or condition that would better be treated by another means or not treated at all.

Evidence for Efficacy of GH Treatment of ISS: The question of whether GH was effective in the treatment of any condition besides GH deficiency was debated for many years. In the medical literature, there are many reports of the use of GH to treat ISS, some of them published many years ago. Early on, the results of these studies often conflicted with each other. However, many of the earlier studies suffered from design flaws, such as too few subjects to make valid conclusions, short duration of follow up, or a relatively low dose of GH. The first long-term study of a large number of subjects using the GH doses typically used

today was published in 1999, by Hintz et al. (See Further Reading) This study showed that children with ISS gained an average of slightly more than 2 inches of adult height after treatment with GH at a dose of 0.3 mg/kg/week for an average of 6 years. There have been other studies published in the years since this report that have come to the same conclusions. Many of these studies were evaluated in a scientific way called a meta-analysis that Finkelstein et al. published in 2002. (See Further Reading) This report looked at the results of 10 controlled trials of GH and 28 uncontrolled trials. Overall, GH treatment appeared to increase adult height by 5-6 cm, or slightly more than 2 inches. Based on this body of medical literature, most physicians accept that GH causes children with ISS to grow taller than they would if they were not treated. The larger question that is still being debated is not whether GH will make someone taller, but who should receive treatment. Should GH be reserved for those children who are the shortest of the short or should it be available to children who are only an inch or two below their peers? Should it be available to athletically talented children to allow them to compete on a higher level, even though their heights are not below average? The extreme high cost of years of treatment with GH has resulted in restrictions of its coverage by insurance companies and other agencies. While this has had the effect of making GH inaccessible for many children who would clearly benefit from treatment, it has also limited its use in situations that many would agree are inappropriate.

FDA-approved Indication: In 2003, the FDA approved GH for treatment of children with ISS whose height standard deviation scores are less than or equal to -2.25 and whose growth rates are too low to allow them to attain normal heights. This would include the shortest 1.2% of boys and girls. In adults, a height standard deviation score of -2.25 is equal to a height of 5'3" in males and 4'11" in females. The FDA's decision has had the effect of providing guidance for the above issues to families, physicians, and payers. However, it has also placed some limits on treatment due to the reluctance of insurance companies to cover GH in some situations in which it is likely to be beneficial. Some payers have made the decision to uniformly deny coverage for GH treatment of all children under the ISS indication. However, GH has clearly been accepted by the medical establishment as being beneficial for some short children.

What to Expect from GH Treatment of ISS

Administration: Growth hormone is administered by an injection under the skin with a thin, short needle. It is generally given on a daily basis. The needles used are the same as those used to give insulin to a diabetic. After beginning GH shots, most children find that the shots are not nearly as bad as they had feared. Unlike an immunization, in which the medication is injected into a muscle, GH is given just under the skin. This allows for a shorter needle and does not cause the muscle tenderness common after immunizations. Most brands of GH have injection devices, often called "pens," which make giving the shots easier and quicker. Research is ongoing in the development of alternative forms of GH that can be given either less frequently or by a different route, such as by inhalation.

Doctor Visits: Your child has probably already been seen by an endocrinologist who has spoken with you and your child, examined him or her, and done a number of different laboratory and x-ray studies. All of this is aimed at determining the cause of his or her growth problem. Once your child has been determined to have ISS and the decision to treat with GH has been made, further visits will be aimed at seeing how well he or she responds to GH and ensuring that there are no complications of treatment. Most endocrinologists see their patients receiving GH every 3-6 months for office visits. At these visits, he or she may ask about any recognized side effects of GH treatment, such as headache, pain in the hip or leg, or problems with the injections. If the child is approaching the age of puberty, the stage of sexual development may also be part of the discussion. The doctor will examine your child, again with attention being paid to his or her pubertal status. Most endocrinologists will periodically obtain an x-ray of the hand to assess the child's bone age. This is useful to judge how effective GH treatment will be in increasing adult height. Because adult height is reached when a girl's bone age is 14-15 years and a boy's bone age is 16-18 years,

the more delayed or the more slowly advancing the bone age is, the more time is available to improve adult height. For some children, the doctor may also periodically obtain blood tests to help judge the effectiveness of GH treatment or to look for problems resulting from treatment. These tests may include measurement of IGF-1, tests of thyroid function, or assessment of blood sugar levels.

Response to Treatment: Although the average child treated with GH gains approximately two inches of adult height, the actual response will vary from child to child. Some children seem to have very little increase in growth rate, while others grow very rapidly and clearly have major increases in their adult heights compared to untreated children. Unfortunately, it is difficult to predict which child will respond well and which one will not. It appears that the child's response to GH during the first year of treatment predicts how he or she will grow for the rest of the treatment course. Often, when a family and their endocrinologist make a decision to treat a boy or girl with GH, it will be made on a trial basis, with a plan to evaluate the response to GH after a year. If there is an increase in growth rate, the child will likely receive long-term benefit from continued treatment. However, if there is no increase in the growth rate, further treatment is likely to be of little benefit and of great cost.



The reasons why some children respond well and others respond poorly are often not clear. The most important reasons are likely related to the child's underlying growth disorder. Is there a problem with his or her ability to respond to natural GH secretion? If so, administration of GH by injection is unlikely to be of additional benefit, as the body may be relatively resistant to any form of GH. The cause of this relative resistance may be a previously undiagnosed condition such as kidney disease, a developmental abnormality of bone formation, one of many genetic abnormalities in the pathway linking GH secretion to GH response or many other reasons. If recognized, some of these conditions can be effectively treated, often leading to an improvement of growth, either with or without GH administration. However, because our understanding of exactly how GH actually results in growth, many of the factors leading to a poor response remain unknown.

When beginning on a course of GH treatment, many parents want to know how long their son or daughter will be taking the medication. If the response is good, most endocrinologists recommend continuing treatment until the child's growth rate naturally levels off in the teenage years, usually around age 14-15 for girls and 16-18 for boys. For individual teenagers, the exact age at which adult height is reached will vary considerably, mainly related to variations in the timing of puberty. Children who begin puberty early usually reach their adult height early, while those who enter puberty later, generally grow for a longer time than their peers. Delayed puberty is a common, but not universal, finding in children with ISS.

Conclusions: In order to ensure that a child is growing normally and to identify those children who are not, regular checkups with the child's pediatrician or family doctor are essential. Careful, accurate measurements of height and the consistent use of published standard growth charts help to understand how a child's height compares to that of his or her peers. Once identified, the abnormally growing boy or girl should be examined by a physician experienced in the evaluation of growth disorder. If the child is found to

have idiopathic short stature, treatment with GH may be an option. The family should discuss this option with an endocrinologist who has expertise in the care of children to see if GH would be appropriate. Growth hormone treatment has been shown to be safe, and in many short and slowly growing children, it may be effective in increasing adult height.

Further Reading:

1. Patterns of Growth
2. Short and OK
3. Hintz RL, et al. Effect of growth hormone treatment on adult height of children with idiopathic short stature. *New England Journal of Medicine*, 1999; 340:502-507.
4. Finkelstein BS, et al. Effect of growth hormone therapy on height in children with idiopathic short stature: A meta-analysis. *Archives of Pediatric and Adolescent Medicine*, 2002; 156:230-240.
5. Leschek EW, Rose SR, Yanovski JA, Troendle JF, Quigley CA, Chipman JJ, et al. Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. *J. Clin Endocrinol Metab*, 2004; 89 (7): 3140-3148.

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