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Persistent Short Stature, Other Potential Outcomes, and the Effect of Growth Hormone Treatment in Children Who Are Born Small for Gestational Age

Peter A. Lee, MD, PhD; James W. Kendig, MD; and James R. Kerrigan, MD

ABBREVIATIONS. SGA, small for gestational age; AGA, appropriate for gestational age; LMP, last menstrual period; SD, standard deviation; GH, growth hormone; SDS, standard deviation score; IUGR, intrauterine growth retardation; VLBW, very low birth weight; IGF-I, insulin-like growth factor-I; IGFBP, insulin-like growth factor-binding protein; RSS/PSS, Russell-Silver syndrome/primordial short stature; ISS, idiopathic short stature.

Normal embryonic and fetal growth proceeds at a predictable rate throughout pregnancy. The predictability of normal intrauterine growth across similar populations at comparable altitudes has permitted the development of standardized reference curves that can be used to compare certain physical characteristics of the newborn according to estimated gestational age. These curves are then used to determine whether the newborn is small for gestational age (SGA), appropriate for gestational age (AGA), or large for gestational age.

Reduced ambient oxygen at high altitude slows gestational growth, so standards are different from those at sea level. In 1966, Lubchenco et al¹ published intrauterine growth curves of white infants, predominantly from the middle and upper socioeconomic classes, who were born in Denver at 5000 feet above sea level. Data included birth weight, head circumference, and crown-heel length of newborns from 26 to 42 weeks' gestational age, as estimated by the day of onset of the last menstrual period (LMP). From this information, fetal growth curves were drawn for the 10th, 25th, 50th, 75th, and 90th percentiles.

In 1969, Usher and McLean² published intrauterine growth curves for a sample of white infants who were from widely varying socioeconomic backgrounds and born in Montreal at an altitude of 100 feet above sea level. Birth weight, birth crown-heel length, head circumference, and 5 additional vari-

ables of newborns from 25 to 44 weeks' gestational age were collected. From the data, these researchers drew fetal growth curves that presented mean values \pm 2 standard deviations (SD), which correspond approximately to the 97th and the 3rd percentiles for birth weight, length, and other measures against gestational age. Because of the difference in birth size for those born at higher altitudes, the Usher and McLean data are applicable to a greater portion of the population in North America than are the Lubchenco data.

Careful measurement of birth length and weight is necessary for establishing whether a newborn is SGA, AGA, or large for gestational age, but accurate gestational dating is the main prerequisite.³ The most precise dating method is serial ultrasonographic measurements, including estimates of fetal weight, head circumference, and abdominal circumference, beginning at 8 to 13 weeks' gestation. LMP, fundal height measurements, and detection of the fetal heartbeat are less accurate ways to assess gestational age.

Accurate diagnosis of SGA is particularly important not only because SGA newborns are at increased risk for perinatal morbidity and mortality⁴⁻⁹ but also because these infants are at increased risk for long-term sequelae. The potential long-term adverse outcomes of SGA birth include persistent short stature and the psychosocial disadvantages associated with short stature in general¹⁰⁻²¹ and specifically with short stature in children who are born SGA and fail to catch up.²²⁻³¹ These psychosocial disadvantages, which include peer-group alienation, low self-esteem, impaired social dynamics, behavioral problems, and lower educational achievement and professional success, together with failure to achieve catch-up growth provide a rationale for treating short children who are born SGA with growth hormone (GH). Two publications suggest that GH therapy may ameliorate these psychosocial effects.^{32,33}

Other potential consequences of SGA birth include adverse neurodevelopmental outcomes^{23,24,26,34-36}, increased insulin resistance³⁷; dyslipidemia³⁸; and a metabolic syndrome (syndrome X) that consists of type 2 diabetes, hypertension, and obesity.³⁹ No data are available to indicate whether GH treatment affects these consequences. This article reviews SGA birth and addresses the rationale for GH therapy in children who are born SGA.

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Definition

SGA has been defined in various publications in different ways, including birth weight or length below the 10th percentile, 5th percentile, or 3rd percentile for gestational age, making it difficult to standardize incidence and prevalence data. For example, the Third National Health and Nutrition Examination Survey, which defined SGA as birth weight below the 10th percentile for gestational age, found the prevalence of SGA in a sample population of infants and children between 2 and 47 months to be 8.6%.⁴⁰ Lower prevalence data would have been reported if SGA had been defined more strictly.

A recommended definition is that used by Usher and McLean²: birth length and/or weight below an SD score (SDS) of -2 (ie, less than third percentile). Using this definition, Albertsson-Wikland and Karlberg⁴¹ reported that 3.1% of infants who were born at term in Sweden between 1973 and 1975 were of low birth weight, 3.5% were of low birth length, and 1.5% were of both low birth weight and low birth length.

SGA is a statistically descriptive term that correlates birth length and/or weight with gestational age and is, therefore, a postpartum diagnosis. It does not refer to fetal growth, although it may be a consequence of diminished fetal growth. In contrast to SGA, the terms intrauterine growth restriction and/or intrauterine growth retardation (IUGR), which are often used interchangeably with SGA, suggest that intrauterine growth has been documented to be insufficient. To document adequately impaired fetal growth and a diminished growth velocity in utero, at least 2 intrauterine size assessments must be performed.⁴² Thus, IUGR should be considered a prenatal diagnosis, currently based primarily on serial measurements of fetal ultrasound parameters.⁴³

Selection of the most useful single biometric parameter depends on the timing and purpose of measurement; crown-rump length is the best parameter for early dating of pregnancy, whereas biparietal diameter maintains the closest correlation with gestational age in the second trimester. When ultrasound rather than LMP is used to determine gestational age, birth weight percentiles are lower early in gestation and greater late in gestation. Accordingly, as the institutional use of ultrasonography rather than LMP for gestational dating has increased, there has been a decrease in the mean gestational age by approximately 1 week, accompanied by a recorded increase in the preterm delivery rate.⁴⁴ Ideally, intrauterine growth curves that are based on ultrasonographic dating rather than LMP should be developed and used when gestational age is assessed by ultrasonography.

Epidemiology

There are no good data for the estimation of the prevalence of SGA. Data provided by the Centers for Disease Control and Prevention's National Center for Health Statistics indicate that there were 4 058 814 live births in the United States in 2000, 7.6% of which were low birth weight (<2500 g) and 1.42%

were very low birth weight (VLBW; <1500 g).⁴⁵ The percentage with low birth weight is substantially higher for black infants: 13.1%. The National Center for Health Statistics, however, does not provide data on birth length or gestational age, making it impossible to determine what percentage of low-birth weight infants were premature, SGA, or AGA.

Furthermore, the intrauterine growth curves used to classify neonates as SGA or AGA were developed during the 1960s using ethnically homogeneous populations.^{2,46} Because the data on which these curves were based have been extrapolated to the general population, the curves are inherently less than accurate when applied across specific population groups and now may result in misleading gender- and race-specific diagnoses of SGA birth.⁴⁷ For example, Davies et al⁴⁸ reported in 1982 that Asian infants who were born in Leicester, United Kingdom, were lighter, shorter, and leaner and had smaller heads than their white counterparts. More recently, Rodrigues et al⁴⁹ found that the prevalence of SGA birth among infants who were born between 1989 and 1992 at a Portuguese hospital was significantly higher ($P < .005$) using local standards for gestational age (9.9% or 10.0%) than the prevalence obtained using standards developed in the 1960s (4.4%). Although the Centers for Disease Control and Prevention recently published revised pediatric growth curves for the United States that more accurately reflect the nation's cultural and racial diversity,⁵⁰ there has been no coordinated effort to revise similarly intrauterine growth curves.

Goldenberg et al⁵¹ found substantial variation in the standards for diagnosis of SGA in the United States. Because there is no average population from which to derive the percentiles used to define SGA, the birth weights that serve as the cutoff point in various published studies may differ by up to 500 g at term and by more than that at 32 and 36 weeks' gestation. The need for intrauterine growth curves based on standard US reference populations is apparent. In 1995, Zhang and Bowes⁵² attempted to develop such curves, describing patterns of birth weight for gestational age (based on LMP) by race, gender, and parity in the US population. These researchers reported that birth weight percentiles were elevated in preterm births and lowered in postterm births when LMP was used to estimate gestational age. However, ultrasound examination is likely to create the opposite effect, lowering birth weight percentiles early in gestation and increasing the percentiles late in gestation, as noted above.

Fetal Growth

First-trimester ultrasonographic studies indicate an increase in linear growth rate beginning between 9 and 10 weeks, which is consistent with a shift to growth from organogenesis.⁵³ By the end of 12 weeks, the crown-rump length doubles from its measurement at 9 weeks.⁵⁴ Between 17 and 20 weeks, the growth rate begins to slow, although the crown-rump length still increases by 50 mm during this 3-week period. Analysis of fetal growth data shows that the decrease in growth rate occurs over a num-

ber of days to become a constant positive value until term.⁵⁵ This plateauing of fetal growth may reflect the effects of the change in the fetal-placental weight ratio.⁵⁴ By term, 6.5 to 7 g of infant are supported by each gram of placenta, whereas at 26 weeks, the ratio is closer to 3:1.

Normal fetal growth can be reduced by maternal, fetal, or placental factors, acting either alone or together (Table 1).^{56–59} Maternal factors include cigarette smoking, which more than any other factor has been strongly linked with fetal growth restriction.⁵⁶ Ahluwalia et al⁶⁰ found that the presence of multiple maternal lifestyle and psychosocial risk factors, such as smoking, alcohol use, and stress during pregnancy, was associated with an increased likelihood of delivering an SGA infant. The most significant individual risk factor was smoking, with a relative risk of 3.27. Another study reported that cigarette smoking during pregnancy was associated with a relative risk of 2.4 for delivering an SGA infant.⁵⁹ Although specific risk may vary among study populations, approximately 40% of all cases of IUGR

seem to be a consequence of maternal cigarette smoking.⁵⁶

Metabolic Characteristics and Pathophysiology of SGA

Hormonal Factors and Fetal Growth

GH is detectable in the fetal pituitary as early as 12 weeks' gestation, and fetal pituitary GH concentrations increase until 25 to 30 weeks' gestation, after which these levels remain constant until term.⁶¹ GH can be identified in fetal serum by the end of the first trimester; GH is secreted episodically, with peak levels of approximately 150 $\mu\text{g/L}$ in midgestation, after which the levels decline.⁶² However, the clinical significance of GH in fetal development in humans is uncertain because hypopituitary newborns have normal birth size.⁶³ Nevertheless, administration of GH and insulin-like growth factor-I (IGF-I) to the mother can affect placental function and thus indirectly influence fetal growth.^{64,65} Curran et al⁶⁶ found that fetal growth was not adversely affected in pregnant GH-deficient women who were not receiving GH replacement therapy.

GH mediates growth by binding to GH receptors, which stimulate the production of IGF-I. IGFs are peptides that are structurally related to insulin,⁶⁷ are synthesized mainly by the liver but also in other tissues, and act in an endocrine and paracrine manner to stimulate cellular growth.^{63,64,67} Studies in animals and humans suggest that IGF-I, unlike GH, plays a crucial role in fetal growth regulation, particularly in later gestation.^{65,67,68} In sheep, the regulation of fetal IGF-I in utero is primarily influenced by placental glucose transfer, which regulates fetal insulin release,⁶⁴ and the glucose/insulin/IGF-I axis is the primary fetal axis involved in prenatal growth.⁶⁴ The importance of IGF-I in human fetal growth was shown by Woods et al,⁶⁹ who described a 15-year-old boy with severe IUGR. Endocrinologic evaluation revealed elevated GH secretion, normal IGF-binding protein-3 (IGFBP-3) levels, and undetectable levels of IGF-I as a result of a homozygous partial IGF-I gene deletion involving exons 4 and 5, which encode a severely truncated and presumably inactive IGF-I peptide.

Numerous studies support the major role played by IGF-I in fetal growth. Mouse studies have shown that knockout of the *Igf1* gene results in a 40% reduction of fetal growth, with growth failure continuing postnatally.^{70–72} In contrast, knockout of the *Igf11* gene results in a similar failure of fetal growth but normal postnatal growth. Knockout of both genes results in comparable growth failure, suggesting that each gene has an independent impact on fetal growth, with a selective IGF-I effect on postnatal growth. There are no comparable data for humans. Mutations of IGF-I are associated with fetal growth failure, independent of GH, but there is no information concerning IGF-II.

Lassarre et al⁷³ measured IGF-I and IGF-II concentrations in sera obtained by cordocentesis between 20 and 37 weeks' gestation from 103 normal fetuses and 16 fetuses with IUGR. With body weight (either measured at birth or estimated from ultrasonographic

TABLE 1. Factors Associated With IUGR^{56–59}

Maternal	
Pregnancy	
	Parity (nulliparity, grand multiparity)
	Age (<16 y, >35 y)
	Previous low birth weight/SGA infant
	Multiple gestation
	Low prepregnancy weight/low weight gain during pregnancy
	Short interpregnancy interval (<6 mo)
	Unintended pregnancy
Medical conditions	
	Malnutrition/malabsorption
	Hypoxemia (chronic pulmonary disease, anemia, cyanotic heart disease, high altitude)
	Hypertension (chronic, preeclampsia)
	Chronic renal disease
	Collagen vascular diseases
	Infection (particularly toxoplasmosis, rubella, cytomegalovirus, herpesvirus)
Substance abuse/drugs	
	Cigarette smoking
	Alcohol
	Opioids
	Antimetabolites/antineoplastic agents
	Anticoagulants
	Anticonvulsants
Fetal	
Chromosomal abnormalities	
	Autosomal trisomies (21, 18, 13)
	Monosomy X (Turner syndrome)
	Deletions (4p-, 5p-, 13q-, 21q-)
Genetic defects (achondroplasia, inborn errors of metabolism)	
Congenital anomalies (microcephaly, anencephaly, cardiovascular defects, ventral wall defects, genitourinary defects)	
Infections (cytomegalovirus, rubella, herpes simplex, varicella-zoster, syphilis, listeriosis, toxoplasmosis, malaria, Chagas disease)	
Placental	
	Insufficiency
	Infarction
	Abruption
	Placenta previa
	Structural anomalies (single umbilical artery, velamentous umbilical cord insertion, bilobate placenta, placental hemangiomas)

data) as the index of fetal size, IGF-I levels were significantly higher in fetuses with weights above the mean for gestational age than in fetuses with weights below the mean ($P < .001$), whereas IGF-II levels were comparable in the 2 groups. In addition, IGF-I (but not IGF-II) levels in fetuses with IUGR were significantly lower than those in normal fetuses of the same gestational age ($P < .01$). Similarly, Leger et al measured serum levels of GH, IGF-I, IGF-II, and IGFBP-3 obtained by cordocentesis during the second half of pregnancy from 166 fetuses with normal growth and from 64 fetuses deemed to have IUGR on the basis of prenatal and neonatal measurements.⁷⁴ Serum IGF-I levels but not GH, IGF-II, or IGFBP-3 levels were significantly lower in the IUGR group ($P = .001$). The incidental presence of fetal malformations in either group had no apparent effect on these hormone levels. Nieto-Diaz et al⁷⁵ obtained umbilical cord blood from 45 normal newborns and 31 IUGR newborns and found that IUGR fetuses had significantly lower-than-normal IGF-I levels ($P < .05$) and higher-than-normal GH levels ($P < .05$) at term. In contrast, placental production of IGF-I and GH may be similar in IUGR, as shown by Sheikh et al,⁷⁶ who studied the expression of GH and IGF-I in term placentas of 10 normal and 15 IUGR births. These investigators found that IUGR placentas showed increased expression of both GH and IGF-I compared with normal placentas at term and speculated that this increased transcription occurred in response to the reduction in fetal growth.

Hormonal Status of SGA Infants and Children

It has been hypothesized that IUGR is a syndrome characterized by relative resistance to a number of hormones, including GH, IGF-I, and insulin.⁶⁴ Consequently, the pathophysiology of persistent short stature in children with IUGR may be similar to that seen in some children who have idiopathic short stature and partial insensitivity to GH.⁷⁷ Such resistance, if a primary defect, may be the basis for an alteration of endocrine programming resulting in SGA being associated with not only postnatal growth failure but also possibly an increased risk of a metabolic syndrome involving obesity, type 2 diabetes, hypertension, and hyperlipidemia in later life.⁶⁴ This is consistent with the so-called Barker hypothesis,⁷⁸ which suggests that in utero imprinting may occur, resulting in resistance to multiple hormones. Such hypotheses seem to involve only subsets of the SGA population. If correct, then persistent short stature in children who are born SGA may be a manifestation of GH or IGF-I resistance.

Normally, mean peak serum levels of GH decrease from 25 to 35 $\mu\text{g/L}$ in the neonatal period to 5 to 7 $\mu\text{g/L}$ through childhood and early puberty, and then peak levels increase again during adolescence.⁶² Although the majority of short children who were born SGA have laboratory evidence of normal GH secretion, some meet the criteria of GH deficiency^{79–84} and/or have abnormal patterns of GH secretion.^{79,81,82,84,85} Although most studies have reported that GH secretion is variable, Boguszewski et al found that children who were born SGA and are still

short at or after 2 years of age spontaneously secrete less GH than do healthy children of short stature who were born AGA.⁸³ Because low serum IGF-I levels have been reported, indicating GH deficiency in short children who were born SGA,⁸⁵ assessment of the IGF axis, with particular attention to IGF-I, has been recommended in these children.⁸⁶

Other mechanisms may explain persistent short stature in children who were born SGA and have normal GH secretion. Partial receptor insensitivity to GH has been demonstrated in some children with idiopathic short stature and normal GH secretion,⁷⁷ and a similar mechanism may be responsible for persistent short stature in some SGA children with normal GH secretion. Assessment of IGF receptor binding among children with IUGR has led to the identification of a subgroup of children with low IGF-I levels, low receptor affinity, and increased receptor numbers. This group differs from a second group characterized by normal IGF-I levels and normal receptor function.⁸⁷ In addition, it has been found that some short children who were born SGA and have normal GH secretion require higher GH-induced serum IGF-I levels to achieve a growth velocity similar to that of GH-deficient children.⁸⁸ These children seem to be partially IGF-I resistant. The mechanism may be an IGF-I receptor defect or a post-receptor-mediated defect. Short, non-GH-deficient children who were born SGA and treated with high-dose GH were found to have a gain in height SDS that was significantly and inversely related to baseline peak overnight (ie, endogenous) GH ($P = .0008$) and fasting IGF-I ($P = .009$) and insulin levels ($P = .014$).⁸⁹ Children with either low serum IGF-I levels or evidence of partial IGF-I resistance may require GH doses higher than the usual GH replacement doses for treatment of short stature. Because short SGA children are candidates for GH therapy, GH stimulation testing is not clearly indicated unless GH deficiency is suspected. However, the measurement of IGF-I levels is appropriate in short SGA children because these levels may suggest resistance and serve as a reference for subsequent monitoring.

Recently, the relationship between the IGF/IGFBP axis and insulin secretion in short children with IUGR has been examined.⁹⁰ Compared with short normal prepubertal children, height- and weight-matched short prepubertal children with IUGR had significantly higher plasma levels of fasting insulin ($P < .004$) and of IGF-I ($P < .0001$), IGF-II ($P < .008$), IGFBP-3 ($P < .0005$), and insulin ($P < .008$) during an intravenous glucose tolerance test. This led to the speculation that hyperinsulinism secondary to insulin resistance may have led to these changes to the IGF/IGFBP axis in the IUGR group. Conversely, to determine whether hyperinsulinemia and increased insulin resistance could be related to persisting abnormalities of the GH/IGF-I axis in children who were born SGA, researchers assessed overnight GH secretory profiles and measured fasting glucose, insulin, intact and 32,33 split proinsulin, and IGF-I levels in short SGA children and short normal-birth weight control subjects.⁹¹ Compared with control subjects, short SGA children had significantly ele-

vated fasting insulin levels ($P = .02$) and reduced insulin sensitivity ($P = .01$), which were related to significantly elevated levels of overnight GH secretion ($P = .01$). The investigators hypothesized that resistance to the somatotropic actions of GH and IGF-I in short SGA children may contribute directly to reduced insulin sensitivity. Thus, although there is evidence of relative GH, IGF-I, and insulin resistance among some SGA patients, the incidence of significant resistance and the precise cause(s) or pathophysiology is as yet unclear.

Natural History

Catch-up Growth in Height

Catch-up growth generally has been defined as a height velocity greater than normal after a period of growth inhibition,⁹² the effect of which is to raise the child's height toward what he or she would have attained if growth had not been inhibited. With respect to a short child who was born SGA, catch-up growth is considered to have been achieved when the child's height becomes ≥ 2 SD below the mean for age. This definition does not address the child's genetic growth potential, which may be considerably greater than -2 SD. Accordingly, lack of catch-up growth in a short child who was born SGA may be defined as a height that remains below -2 SD for age.

Persistent Short Stature

Defining catch-up growth as a height velocity above the statistical limits of normal for gender and age and/or maturity during a defined period of time after a period of growth inhibition, Karlberg and Albertsson-Wikland^{93,94} assessed the incidence and relative risk of persistent short stature among SGA infants (defined by a birth length < -2 SD) in a cohort of 3650 healthy, full-term singleton newborns. In this cohort, most of these infants showed catch-up growth during the first 6 months after birth, and by 1 year only 13.4% remained below -2 SDS in height. During childhood, almost half of those still short attained catch-up growth, so that at 18 years, 7.9% remained short. Therefore, although the majority of SGA infants catch up during infancy, approximately half (8%) will never catch up and will remain short as adults. In summary, approximately 92% of otherwise healthy, full-term singleton infants with birth length below -2 SDS will achieve catch-up growth in length, usually during the first year of life. Conversely, this report suggests that children who are born SGA and do not show postnatal catch-up growth and remain short at 2 years are at high risk for short stature in later life. The relative risk of short stature at 18 years is 7.1 if SGA is based on length and 5.2 if SGA is based on weight.⁹⁵ When assessing the group of children who have not caught up, it is important to consider genetic height potential, because a portion of these children may have genetic short stature based on parental height.

When SGA or failure to catch up was defined differently, different results were reported, not unexpectedly. McCowan et al,⁹⁶ defining SGA as birth

weight below the 10th percentile for gestational age, reported that 20% of 203 SGA infants remained short at 6 months. Hediger et al,⁴⁰ also defining SGA as birth weight below the 10th percentile for gestational age, noted that after an initial period of catch-up growth, the mean height of infants born SGA can be expected to remain at approximately the 25th percentile through early childhood with a mean deficit of almost 3 cm at 4 years. Among children who are born SGA and do experience catch-up growth, height deficits persist and improve only minimally during childhood. Height deficits for age were -0.66 SDS at ages 3 to 4 years,⁴⁰ -0.57 SDS at ages 6 to 7 years,⁹⁷ and approximately -0.5 SD at 7 years.²⁵ As with any short child, it is pertinent to consider familial height, because short stature is not necessarily abnormal and treatment is not necessarily indicated.

RATIONALE FOR TREATING SHORT CHILDREN WHO WERE BORN SGA

In July 2001, the Food and Drug Administration approved recombinant human GH for the long-term treatment of growth failure in children who were born SGA and fail to manifest catch-up growth by age 2. The basis for treatment after 2 years of age is the evidence that height is not likely to normalize spontaneously after this age. Thus, children who are older than 2 years should be considered for therapy if they do not have evidence of ongoing catch-up growth and if greater height for age would be expected on the basis of family heights. Dosing is approved up to 0.48 mg/kg body wt/wk. The rationale for GH therapy is primarily to increase linear growth rate in short children who were born SGA and have persistent short stature so that they may attain a height within the normal range for gender and age and ideally within the target height percentile range. Therapy may prevent life-long detrimental quality-of-life issues associated with short stature. Long-term outcome data will be necessary to determine whether GH treatment will affect metabolic and neurodevelopmental outcomes, as well as to document adult heights.

Increasing Childhood and Adult Height

The use of GH to increase the height of healthy short children remains controversial.⁹⁸ Although GH therapy has been used in a large number of non-GH-deficient short children, outcome data are limited and treatment has not been consistent. Access to treatment often depends on the type of insurance coverage that the patient has.⁹⁹ In addition, parents' attitudes and preferences may affect the decision-making process of pediatricians.¹⁰⁰ An extensive discussion of these issues is beyond the scope of this article. It is clear that greater and greater numbers of short children who do not have a diagnosis of GH deficiency are being treated. This includes children with idiopathic short stature, familial short stature, and growth failure as a consequence of chronic disease, going beyond those conditions for which GH is approved such as Turner syndrome, chronic renal failure, Prader-Willi syndrome, and now SGA. Side effects of GH therapy do not occur more frequently

among these children than among GH-deficient children.

It has been apparent for years that height discrimination, independent of the underlying cause of short stature, begins in childhood and height hierarchies are established early, with the connection between height and status being cross-cultural.^{101,102} For example, one recently published report suggests that short children are more likely to be bullied in school than their taller classmates.¹⁰³

For those pediatricians and parents who may consider GH therapy for SGA children with persistent short stature, the current clinical literature supports the efficacy and safety of GH for normalization of height during childhood of short children who were born SGA.^{80,82,104–119} Treatment among most may have been begun by 3 years of age, because the growth response to GH is better at younger ages.¹⁰⁵ However, treatment should not be initiated until spontaneous catch-up growth, if any, is complete.

In the usual assessment of growth potential, skeletal age delay is considered to correlate with the anticipated degree of catch-up growth. However, among children who were born SGA and have not been treated with GH, delay of bone age has not been correlated with more growth or taller adult height.⁴² It seems that delay in skeletal age disappears quickly with the initial exposure to sex steroids at the onset of puberty without concomitant increase in height. Thus, although a delay in skeletal age can be considered to be consistent with the expectation of catch-up growth for the prepubertal child, skeletal age should not be a major criterion when deciding whether to begin a trial of GH therapy. Children without skeletal age delay have experienced substantial increases in growth rate on GH therapy, with skeletal maturity advancing somewhat.¹⁰⁵

Data with respect to adult height in short children who were born SGA and were treated with GH are limited. It is unclear whether there is a dose relationship to adult height after long-term therapy, although interim data suggest that there may be a direct relationship. Ranke and Lindberg¹¹⁶ treated 16 short children who were born SGA to above target height with GH at a median dose of 0.24 mg/kg/wk. Another study used a low mean GH dose of 0.14 mg/kg/wk to treat 70 children with IUGR.¹²⁰ Treatment with this relatively low dosage of GH was associated with a gain of 0.6 SDS, suggesting a final height gain of only 3.4 cm.

The following 3 studies are representative of efficacy and safety trials. The effects of GH over 2 years in 69 non-GH-deficient children who were born SGA have been assessed by Butenandt and Lang.¹⁰⁴ At entry, the children had a mean age of 5.1 years, mean bone age of 3.8 years, and mean height SDS of -4.0 . The children were randomly assigned to receive no treatment ($n = 20$) or daily subcutaneous injections of GH at a dose of 0.24 ($n = 24$) or 0.48 mg/kg/wk ($n = 25$). Mean height velocity SDS after the first year of treatment was -1.2 ± 1.6 in the control group, 2.8 ± 2.3 in the 0.24-mg/kg/wk group, and 5.5 ± 2.7 in the 0.48-mg/kg/wk group (Fig 1). Corresponding values during the second year were -0.9 ± 1.4 , $1.6 \pm$

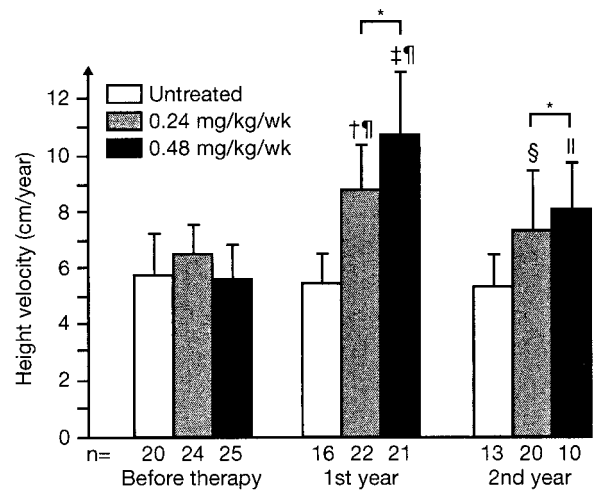


Fig 1. Height velocity SDS (mean \pm SD) before GH treatment and after 1 and 2 years in the study for 69 non-GH-deficient children who were born SGA. A significant increase in height velocity was seen in treated patients compared with untreated patients (controls): * $P < .001$, both treated groups versus controls; † $P < .003$ vs controls; ‡ $P < .001$ vs controls; § $P < .02$ vs controls; ¶ $P < .002$ vs controls; ¶ $P < .02$ between dosage groups. (Adapted from Butenandt O, Lang G. Recombinant human growth hormone in short children born small for gestational age. German Study Group. *J Pediatr Endocrinol Metab*. 1997;10:275–282. With permission.)

2.2, and 2.9 ± 2.1 . A significant difference was observed between the control group and the treatment groups for each year and between the 2 treatment groups during the first year. Catch-up growth (defined as height velocity 1 SD above the mean) was achieved in 86% of the 0.24-mg/kg/wk group and 95% of the 0.48-mg/kg/wk group during the first year of treatment; it was maintained in 65% and 79%, respectively, during the second year. Treatment was well tolerated, with no clear trends in any laboratory values, including those assessing carbohydrate metabolism.

A similar study design was used to evaluate the efficacy of GH in 48 short children who were born SGA and who at entry had a mean age of 4.7 years and a mean height SDS of -3.16 ± 0.70 , but the investigators extended the evaluation period to a third year.¹⁰⁵ Twelve children received no treatment, 16 were treated with GH at 0.24 mg/kg/wk, and 20 were treated with GH at 0.48 mg/kg/wk; 42 children completed 2 years of therapy, and 24 treated children continued therapy for a third year. In the untreated group, the mean change in height SDS was 0.07 ± 0.15 during the first year and -0.03 ± 0.12 during the second year, with no growth acceleration during the entire 2-year period. In the group that was treated with 0.24 mg/kg/wk, the mean change in height SDS was 1.09 ± 0.48 during the first year of therapy, 0.45 ± 0.23 during the second year, and 0.18 ± 0.18 during the third year (Fig 2). There was a marked improvement in the change in height SDS for the group that was treated with 0.48 mg/kg/wk: 1.43 ± 0.54 during the first year of therapy, 0.70 ± 0.17 during the second year, and 0.41 ± 0.16 during the third year. After the third year of treatment, the group that received 0.48 mg/kg/wk had achieved its

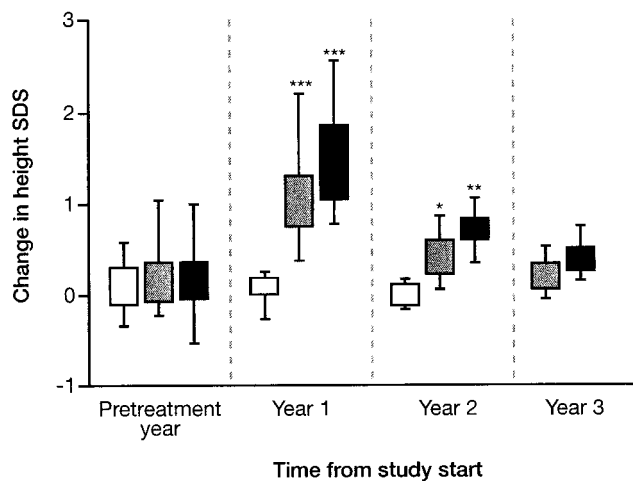


Fig 2. Growth in SGA children, expressed as change in height SDS, during the pretreatment year and the first, second, and third years of GH therapy. Open box, untreated children; gray box, 0.24 mg/kg/wk; black box, 0.48 mg/kg/wk. Boxes indicate lower and upper quartiles; whiskers indicate 1st and 99th percentiles. * $P < .05$, ** $P < .01$, *** $P < .001$ vs the untreated group. (Adapted from Boguszewski M, Albertsson-Wikland K, Aronsson S, et al. Growth hormone treatment of short children born small-for-gestational-age: the Nordic multicentre trial. *Acta Paediatr.* 1998;87:257–263. With permission.)

target height. Bone age maturation was similar in the untreated and GH-treated groups. The major determinants of the growth response were the GH dosage, the age at the start of treatment (the younger the child, the greater the growth response), and the family-corrected individual height deficit (the greater the deficit, the greater the growth response). Treatment was well tolerated. There was a significant, dose-dependent increase in IGF-I and IGFBP-3 levels, and a significant rise in insulin levels was observed after 2 years of GH treatment with 0.48 mg/kg/wk. However, there was no accompanying effect on fasting glucose or glycosylated hemoglobin, indicating the physiologic balance between GH and insulin.

Data from a large number of patients in the National Cooperative Growth Study were reviewed to

evaluate the response to GH treatment in 270 children with short stature associated with unclassified IUGR ($n = 144$) or with Russell-Silver syndrome or primordial short stature (RSS/PSS; $n = 126$).¹⁰⁶ At entry, the mean age was 7.35 ± 4.21 years, the mean bone age was 5.93 ± 4.15 years, and the mean height SDS was -3.49 ± 1.16 for patients with unclassified IUGR. For patients with RSS/PSS, the mean age was 6.31 ± 3.49 years, the mean bone age was 4.91 ± 3.69 years, and the mean height SDS was -3.83 ± 1.05 at entry. All patients were treated with daily subcutaneous injections of GH at a dose of approximately 0.28 mg/kg/wk for up to 4 years. Height SDS improved with each year of therapy. Mean growth rates increased by 3 to 3.5 cm/y in both groups during the first year of treatment (Fig 3). Unclassified patients who had IUGR and completed 4 years of treatment reached a height SDS of -1.32 ± 0.79 , whereas the height SDS of those with RSS/PSS improved to only -2.10 ± 0.99 . In addition, no change occurred in predicted adult heights. Although there was no control group, the investigators noted that there was little reason to expect that height SDS would change over the intermediate term in untreated patients. GH was well tolerated, but only 46% of patients continued treatment through 4 years.

Decreasing Adverse Psychosocial Outcomes Associated With Short Stature

Although some studies have found no association between psychosocial function and short stature in otherwise normal children or adults,^{121–127} other studies support such a relationship.^{10–12,14,17,19–23,25–30} The studies that support an association, excluding those limited to VLBW infants (<1500 g), are summarized in Table 2.

Psychosocial and Cognitive Function in Children Who Were Born SGA

Most studies of the relationship between height and psychosocial or cognitive function were conducted in children with short stature as a result of a

Fig 3. Growth rates in patients with unclassified IUGR and RSS/PSS treated with GH at a dose of approximately 0.28 mg/kg/wk. The growth rates increased by 3 to 3.5 cm/y in both groups of patients in the first year of GH therapy. No significant difference was observed in the growth rate between the 2 groups. (Reprinted from Chernausek SD, Breen TJ, Frank GR. Linear growth in response to growth hormone treatment in children with short stature associated with intrauterine growth retardation: The National Cooperative Growth Study experience. *J Pediatr.* 1996;128:S22–S27, with permission).

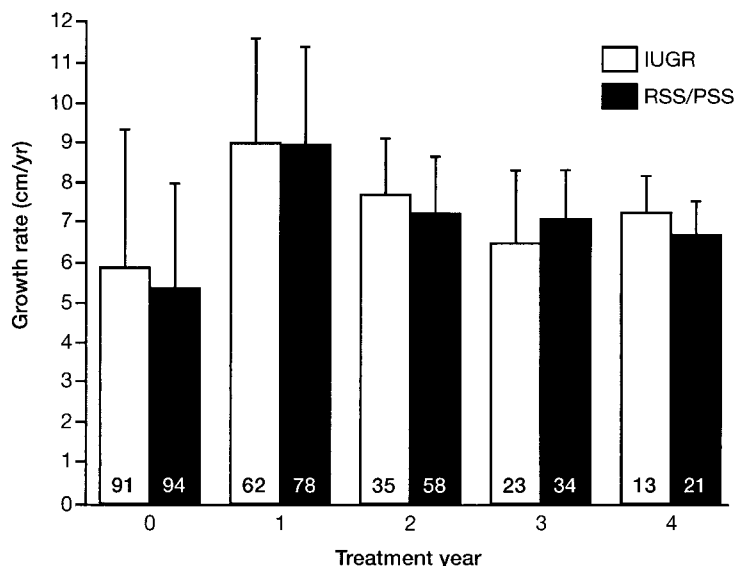


TABLE 2. Adverse Psychosocial Effects of Short Stature

Study Population	Reference	Study Design	Result/Conclusion
Short children born SGA	Andersson et al ²⁶	Fagan Test of Infant Intelligence at 7 mo and Home Screening Questionnaire at 13 mo for SGA and normal infants	SGA infants had significantly ($P < .05$) lower scores, but this may reflect greater vulnerability to adverse social conditions in home
	Larroque et al ²³	Relation between SGA and school difficulties in adolescents and young adults, compared with AGA	Late entry into secondary school more common; higher proportion fail to take/pass baccalaureate examination
	Lundgren et al ²²	Effect of catch-up growth on intellectual/psychological performance of males born SGA	Most important predictor of risk of subnormal performance was absence of catch-up growth
	Paz et al ³¹	Effect of term SGA birth on educational achievement of 17-year-old males	Significantly lower educational achievement compared with AGA 17-year-olds born SGA ($P < .03$)
	Strauss ²⁷	Effect of SGA birth on school performance and achievement at ages 5, 10, 16, and 26 y	Small but significant deficits at 5, 10, and 16 y; lower income and less likely to have professional/managerial jobs at 26 y; SGA subjects significantly shorter than controls
	Strauss et al ²⁵	Effect of IUGR on childhood development, controlling for environmental and genetic factors	Significantly lower IQ and Bender-Gestalt scores ($P < .001$) at 7 y compared with infants without IUGR
	Other short children	Jiang et al ¹⁹	Assessment of potential risk factors for attempted suicide in military-age Swedish men
Rovet and Holland ¹¹		Impact of GH therapy for 2 y on final height and psychological status of girls with Turner syndrome	Correlation between higher growth rate and self-perception of intelligence, attractiveness, number of friends, popularity, and degree of teasing
Stabler et al ¹⁰		Psychological effect of short stature on children 5–16 y old referred for GH therapy	Significant discrepancy ($P < .01$) between IQ and achievement scores, and high rate of behavior problems ($P < .0001$)
Stabler et al ¹²		Intelligence, academic achievement, social competence, and behavior in short children before and during GH therapy	Significantly more behavioral problems in short children ($P < .001$); behavior scores, improved compared with normal-stature control group after 3 y of GH therapy
Stathis et al ²¹		PPVT-R at age 5 y with results correlated with height	Short stature a significant ($P < .01$) predictor for lower PPVT-R scores, independent of psychosocial disadvantage or biological risk factors
Steinhausen et al ¹⁸		Effect of short stature on behavior profiles in children and adolescents	Short stature had significant adverse effect on Child Behavior Checklist and Youth Self-Report scores
The Partnership for Child Development ²⁰		Factors accounting for late enrollment in school in African countries	Short stature strongly associated with late school enrollment independent of socioeconomic status
Zimet et al ¹⁴		Interview and self-report evaluation of short children 5–16 y old referred to endocrinology service	Degree of short stature not related to overall poor psychological functioning, but distress increased with age to adolescence
Zimet et al ¹⁷		Self-report evaluation of short subjects at least 18 y old who had been referred to endocrinology service	Shorter adult stature significantly associated with lower educational achievement ($P < .001$), self-esteem, and greater emotional distress ($P < .01$)

PPVT-R indicates Peabody Picture Vocabulary Test-Revised.

variety of underlying causes, and only some involved SGA children specifically. The following studies were conducted in patients who were born SGA, but the adverse quality-of-life outcomes observed were not necessarily related to persistent short stature.

The relationship between home environment and cognitive ability has been analyzed in 142 SGA infants and 172 AGA controls.²⁶ Infants who were born SGA had significantly lower scores on the Fagan Test of Infant Intelligence at 7 months ($P < .05$) and on the Home Screening Questionnaire at 13 months ($P < .05$). The investigators concluded that SGA infants may be more vulnerable to adverse social conditions than infants who are born AGA and that the cognitive impairment observed may be an effect of both their social environment and their parents' general intelligence.

Various tests to measure cognitive function were used at 1, 2, 3, 5, and 6 years in 129 premature SGA infants and 300 premature AGA infants using age-appropriate tests.²⁴ At each age, cognitive scores were significantly lower among the children who were born SGA ($P < .001$ at 1 year, $P = .002$ at 2 years, $P = .025$ at 3 years, and $P = .005$ at 5 and/or 6 years) and were independent of neurologic status except at 3 years of age. The results indicate that premature infants who are born SGA are at greater risk for adverse cognitive outcomes than premature infants who are born AGA.

Data from the National Collaborative Perinatal Project have been analyzed to compare the intelligence and visual-motor development of children with IUGR with these parameters in normal children.²⁵ IQ scores at 7 years of age were 6.2 points lower and visual-motor development was 5 points lower among children with IUGR ($P < .001$), even when children with birth depression were excluded from the analysis.

The relationship between SGA birth and school performance and learning ability has been studied at ages 12 and 18 years by comparing outcomes for 236 full-term SGA infants with those for 281 full-term AGA infants.²³ After the results were adjusted for other variables, the investigators found that late entry into secondary school and failure to take or pass the baccalaureate (high school) examination were more common among those who were born SGA.

The British Birth Cohort Study data were used to assess school performance and achievement at ages 5, 10, and 16 years and other outcome measures at 26 years of age among 13 125 adults with normal birth weight and 1064 adults who were born SGA in 1970.²⁷ Those who were born SGA had small but measurable deficits in academic achievement at 5, 10, and 16 years. As adults, they were significantly less likely to hold managerial or professional positions ($P < .01$) and reported significantly lower levels of income ($P < .01$) while remaining significantly shorter ($P < .001$) than those with normal birth weight.

A population-based study of 254 426 conscripted 18-year-old Swedish male individuals was performed to determine whether catch-up growth af-

ected intellectual and psychological function in early adulthood.²² In this cohort, 2.5% were born short for gestational age and 2.6% were born light for gestational age. Both low birth weight and short birth length increased the risk for subnormal intellectual and psychological performance on standard tests. The most important predictor of substandard performance was failure to achieve catch-up growth in height. This is the only publication to suggest better outcome of such measures in association with catch-up growth.

Cognitive and academic performance was assessed comparing 17-year-old male individuals who were born SGA or AGA at term by matching neonatal data to the results of intelligence tests performed when the subjects entered the army.³¹ Adult height in these 2 groups was not considered. Those who were born SGA had lower cognitive performance and educational achievements ($P < .03$) than the AGA group.

One study showed a relationship between VLBW (≤ 1250 g) in SGA infants and decreased scores on developmental tests at 1, 2, and 3 years, compared with infants who were born AGA.²⁸ The infants who were born SGA were significantly shorter at 3 years than those who were born AGA ($P < .05$). Another study found that children who were born SGA and had VLBW (< 1500 g) had lower scores on measures of visuospatial ability, nonverbal reasoning, strategy formation, and gross motor coordination at 8.7 to 11.2 years than children who were born AGA.²⁹ The smallest VLBW infants had the highest incidence of behavioral and educational problems. These findings are consistent with the observation that IUGR in VLBW infants has a significant long-term impact and that developmental deficits may become increasingly evident in the early school years. A group of 20-year-olds with a history of VLBW were recently reported to have been less likely to graduate from high school, less likely to be enrolled in postsecondary study, and more likely to have lower academic achievement scores than those who were born AGA.³⁰ However, only 8% of the VLBW male individuals and 11% of the VLBW female individuals studied reported a current height below the third percentile, so the relationship to short stature is unclear.

Effect of GH Therapy for Short Stature on Psychosocial and Cognitive Function

Psychological studies of short GH-deficient children who are referred for GH therapy may show a poor quality of life, which is often a consequence of feelings of anxiety, depression, social isolation, or difficulties maintaining attention.¹²⁸ These difficulties may lead to low academic achievement and poor interpersonal skills. The effect of GH treatment on psychosocial functioning in children with short stature (eg, Turner syndrome) seems to be positive when accompanied by an increase in height velocity,^{129–131} and some improvement in behavior has also been reported after 2 years of GH.^{130,131} Many, however, report poor quality of life during young adulthood despite the achievement of acceptable height,¹²⁸ although this could be at least in part an effect of adult

GH deficiency. Results of studies of quality-of-life endpoints seem to be inadequately evaluated and inconsistent.

Researchers studied the prevalence of behavioral and learning problems among 195 children (mean age: 11.2 years; range: 5–16 years) with short stature caused by GH deficiency or idiopathic short stature (ISS) and a normal-stature matched comparison group.¹² The mean height of 109 children with GH deficiency increased 1.3 SD to -1.28 SDS, and the mean height of the 86 children with ISS increased 1.45 SD to -1.39 SDS. The effect of GH treatment on such problems was also assessed. Child Behavior Checklist scores for total behavioral problems were higher in the children with short stature than in the normal-stature control subjects at baseline, suggesting more problems in the former group ($P < .001$). After 3 years of GH therapy, these scores improved in children with GH deficiency ($P < .001$) and with ISS ($P < .003$). There was also significant improvement in the subscale scores of children in the GH deficiency group (withdrawal, somatic complaints, anxiety/depression, attention span, social problems, and thought problems).

The impact of GH on adult height and psychological status of girls with Turner syndrome has been evaluated by randomization into a GH treatment group and a control group at ages ranging from 7.5 to 12.8 years (mean age: 10.8 years).¹¹ Girls who were treated with GH for 2 years showed a significant increase in growth rate, although the rate declined with continued treatment; the growth rate in the control group remained constant. There was a correlation between growth rates and the girls' perceptions of themselves as more intelligent, more attractive, having more friends, being more popular, and experiencing less teasing in the treated group but not in the untreated group. There was no correlation between growth rate and functioning in school.

The quality of life of 2 groups of children with short stature has been compared by Pilpel et al.¹²⁵ One group ($n = 96$) that was treated with GH for at least 2 years included 15 children with classic GH deficiency, 16 children with Turner syndrome, and 65 children with no underlying disease. At the beginning of treatment, they were at least 6 years of age. The second group ($n = 33$) included children who had short stature with no underlying disease and were not treated with GH. There was no significant difference between the 2 groups in quality of life, as assessed by self-administered questionnaires, with respect to school achievement, leisure activity, emotional and physical self-esteem, or relationship with peers and family.

Psychological testing was used to search for a relationship between GH treatment begun at 7 years of age in a group of 15 short but otherwise normal children.¹²⁴ Results were compared after 3 and 5 years with those in untreated short controls and average-height controls. Only the treated group showed a significant height increase (SDS -2.44 to -1.21 over 5 years; $P < .001$). No significant differences were found at entry, 3 years, or 5 years in IQ, attainment (word reading and basic number skills),

behavior, or self-esteem, although both groups of short children expressed less satisfaction with their height than the average-height controls ($P < .01$).

CONCLUSIONS

SGA should be defined as a birth weight and/or length at least 2 SDS below the mean (-2 SDS) for gestational age. Accurate diagnosis is important because SGA newborns are at risk for increased morbidity and mortality, and SGA children are at increased risk for persistent short stature and associated long-term adverse psychosocial outcomes. There is substantial variation in the standards for diagnosis in the United States, and intrauterine growth curves based on ultrasonographic gestational dating and standard reference populations are needed.

Absence of catch-up growth in a short child who was born SGA may be defined as height remaining at least 2 SD below the mean for age. Approximately 10% of SGA infants do not experience catch-up growth by 2 years of age, but the prevalence of persistent short stature varies with its definition. Children who do not catch up by 2 years are at high risk for short stature in later life. As with any group of short children, not all SGA children who do not catch up to at least the -2 SD point are necessarily short in relation to their genetically expected heights. Children from short families may not be candidates for GH therapy.

GH therapy is effective and safe when administered in doses of 0.24 to 0.48 mg/kg/wk to increase the height of short children who were born SGA. Short children who were born SGA may be partially resistant to GH, which explains the greater effectiveness of the higher dose. Short stature during childhood is associated with adverse quality-of-life outcomes, which may be preventable when growth is accelerated with GH therapy. As data accumulate, outcome in terms of adult heights can be better evaluated.

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