

Safety and efficacy of growth hormone treatment in small for gestational age children

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Purpose of review

Approximately 100 000 infants are born small for gestational age (birth weight <2 standard deviation) annually in the US alone. Because of catch-up growth, 10–20% of all children born small for gestational age will be eligible for growth hormone therapy. Growth hormone has been approved by the Food and Drug Administration in 2003 and by the European Agency for the Evaluation of Medical Products though at different enrollment and treatment criteria. Benefits and risks of growth hormone therapy for small for gestational age children are the purpose of the present review.

Recent findings

Mean height increased by as much as two standard deviation over 3 years of treatment in infants born small for gestational age. Rapid catch-up growth is desirable and will only be achieved with higher growth hormone doses (0.48 mg/kg/week). Treatment should be continuous and not interrupted. The safety profile of growth hormone treatment is excellent. Transient elevation of insulin levels returned to near normal after growth hormone treatment was discontinued.

Summary

Growth hormone treatment in small for gestational age children has been found to be well tolerated and is an important advance in the treatment of short stature in pediatrics. Treatment of short prematurely born infants with growth hormone may offer similar efficacy and safety as growth hormone treatment in small for gestational age infants.

Keywords

catch-up growth, growth hormone, insulin resistance, intrauterine growth retardation, small for gestational age, short stature

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Introduction

Small for gestational age (SGA) is defined as either a birth weight or length or both greater than 2 standard deviation (SD) below the sex-specific population reference mean for gestational age.

Natural history of growth in small for gestational age children

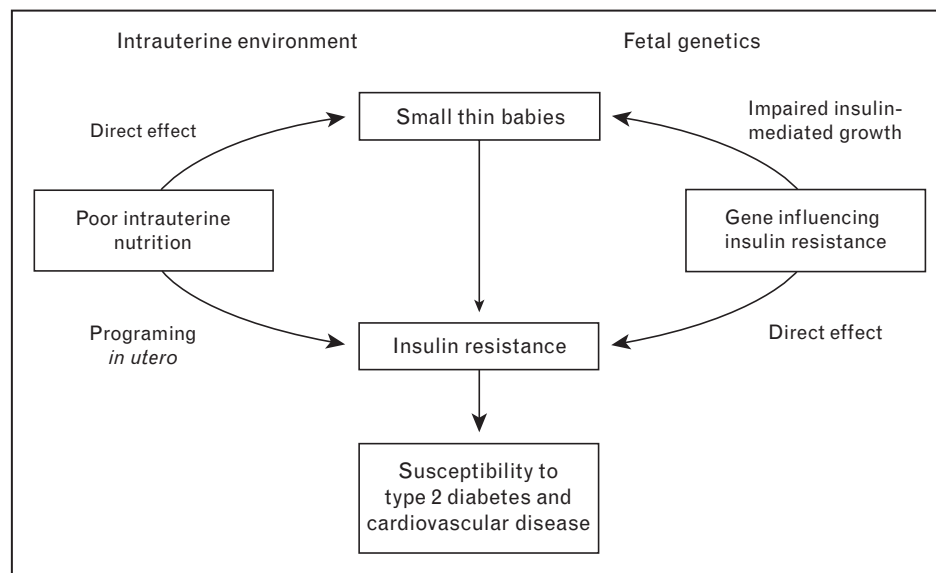
Between 80–90% of full-term SGA infants catch up in height in the first 2 years of postnatal life [1,2]. Premature SGA infants (<37 weeks gestation) may take longer to catch up than full-term infants within this 2-year period [3]. Approximately 10% of children born SGA will remain -2 SD or less for height throughout childhood and adolescence into adulthood [4,5]. Even more significantly, 13.6% of adults born SGA were noted to have a final height more than 2 SD below the mean when measured at

the age of 20–21 years. The relative risk of short stature (<-2 SD) at 18 years of age among children born SGA who do not achieve catch-up growth by 2 years of age is 5.2 for those with low birth weight and 7.1 for those with low birth length [2]. Short adult height is thus one of the most frequent complications of being born SGA, more frequent than even other adult morbidities such as metabolic syndrome [6]. Growth hormone (GH) therapy is indicated in children born SGA who do not achieve catch-up growth by 2–3 years of age in order to attain a normal height in early childhood and maintain normal growth later in childhood [4,5] (Fig. 1).

Growth hormone therapy in children born small for gestational age

The use of GH in short children born SGA has been investigated for nearly 40 years. In July 2001, GH was

Figure 1 Two possible explanations for the association of being born small for gestational age with insulin resistance, type 2 diabetes and ischemic heart disease: intrauterine environment and fetal



approved by the Food and Drug Administration (FDA) at a dose of 0.48 mg/kg/week for the long-term treatment of growth failure in children born SGA who fail to manifest catch-up growth by the age of 2 years. In contrast, the European Agency for the Evaluation of Medical Products (EMA) approved GH for the treatment of children born SGA after the age of 4 years at a dose of 0.22 mg/kg/week. The rationale behind this recommendation is that there may still be a possibility, albeit small, of spontaneous catch-up growth between 2 and 4 years of age, especially in infants born preterm.

Parental height and birth length are the only two variables that seem to be predictive of adult height in untreated children who are born SGA [6]. In GH-treated short children who were born SGA and followed to near adult height, GH therapy effectively increased adult height above predicted height, and patients achieved target height [7].

Endocrine work up of children born small for gestational age prior to growth hormone therapy

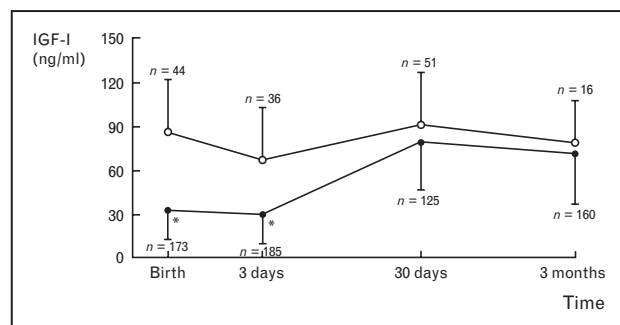
A standard evaluation for short stature is mandatory to rule out specific growth-limiting disorders that may occur with the SGA phenotype. Concomitant conditions like a nutritional deficiency, chronic renal disease, thyroid disease, emotional deprivation, use of growth-inhibiting medications and genetic conditions like Bloom syndrome in which GH therapy is hazardous should be ruled out. Radiological examination of skeletal maturity, though

routinely performed, is an unreliable predictor of adult height in SGA children [8]. Bone maturation may show idiosyncratic variations in untreated SGA children, particularly between 6 and 9 years of age [8,9].

Classic GH deficiency is rare in the SGA population. Mean insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP 3) levels are reduced in children born SGA by approximately 1 SD, but the range of levels is wide indicating a possible heterogeneity in the mechanisms of growth failure from insufficient IGF-1 generation to IGF-1 insensitivity [10]. The status of the GH-IGF axis at birth or in early postnatal life is not predictive of later growth and, therefore, hormone measurements in the SGA infant or child are not indicated in routine care [11]. However, many short patients who were born SGA have diminished GH output as evidenced by low levels of spontaneous GH secretion and depressed circulating levels of markers of GH secretion such as IGF-1 [12–14]. Children born SGA may be partially IGF-1 resistant as evidenced by the fact that they required greater basal and GH-induced plasma IGF-1 concentrations to achieve the same growth velocity as GH-deficient children and those with familial short stature [10] (Fig. 2).

The present recommendation is to perform GH testing when GH deficiency is suspected on clinical or biochemical grounds. Measurement of circulating IGF-1 and IGFBP-3 levels provides a baseline to assess the response to GH therapy and helps screen this population for GH deficiency.

Figure 2 Mean (\pm SD) serum levels of insulin-like growth factor 1 in children born small for gestational age and controls from birth (cord blood measurements) to 3 months of age



Levels of insulin-like growth factor 1 significantly reduced in the cord blood of infants born small for gestational age, but serum insulin-like growth factor 1 levels normalized rapidly after birth. IGF-1, insulin-like growth factor 1; SGA, small for gestational age. Reproduced from [11].

Goals of growth hormone therapy for small for gestational age children

The initial objective is accelerating prepubertal growth to achieve catch-up growth to a normal height in early childhood and to maintain normal growth later in childhood, with the ultimate objective of normalizing adult height as much as possible.

Clinical experience with growth hormone therapy for small for gestational age children

A number of clinical trials have demonstrated that GH safely and effectively induces catch-up growth in short prepubertal children who were born SGA. In a study of children of mean age 4.5 years and severe short stature (>3 SD below mean for chronological age and sex, and birth weight <10 th percentile), GH induced a sustained catch-up growth [15]. All children received a GH dose of 0.48 mg/kg/week for 3 years. Although one of the groups initially underwent a 1-year observation period, there was no clinically observed spontaneous acceleration of height velocity. At the end of 3 years of treatment, mean height SD for chronological age had increased by 2.0 ± 0.7 in the two groups and no adverse events were noted.

Results of three subsequent short-term French studies showed that growth rate increased markedly, nearly doubling after 1 year of treatment with GH doses of up to 0.48 mg/kg/week, which is nearly two times greater than the standard replacement doses used to treat children with GH deficiency [16]. The desired rapid catch-up growth was noted, and mean height increased by nearly 2 SD in the 3-year period.

Studies of long-term treatment with GH, beginning around 8 years of age and continuing for 7–8 years using

doses of 33 or 67 μ g/kg/day (0.22 or 0.48 mg/kg/week), suggest that GH is effective at increasing adult height by 1–2 SDs [17–20]. In a study of GH therapy in Swedish children born SGA, those who started the treatment at least 2 years before the onset of puberty gained a mean adult height SD of 1.7, corresponding with a 12 cm increase in adult height, as opposed to those who started GH therapy at a later age, gaining a mean adult height SD of 0.9, corresponding to a 6 cm increase in adult height [18]. Similarly, studies in which children were started on GH at a mean age of 7.8 years estimated gains in adult height of around 2 SD [17], whereas such estimates were only 0.6 SD in studies in which GH therapy was started at 10–12 years of age [19,21]. It has also been shown that the younger the child at the start of GH therapy, the quicker the initial GH response [22,23].

Thus, it can be concluded that the growth response is better when children begin therapy in early childhood, and that age at the initiation of therapy is a major determinant of the growth response. In addition, target height should be considered, although it should not be used to exclude any child who is SGA and would otherwise be treated for failure to catch up.

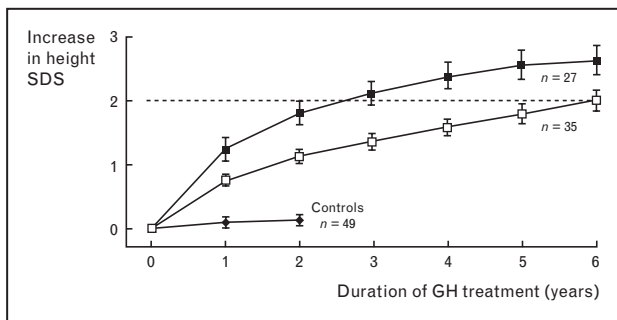
Growth hormone dosing for small for gestational age children

The dose of GH is the most important predictor of the growth response to therapy during the first year of treatment among children born SGA [24]. A recent meta-analysis of adult height data from published clinical trials showed that in children born SGA in whom GH therapy is initiated at a mean age of 5 years, a dose of 0.48 mg/kg/week for 10 years elicits gains in adult height SD that are about 0.4 SD greater than those achieved with a lower dose of 0.22 mg/kg/week [25], suggesting that early catch-up growth requires higher doses of GH. Although one study carried to final height suggested that no dose difference was seen, this would have to be confirmed in other trials [19]. Zucchini *et al.* [26] found that GH at a dose of 0.23 mg/kg/week for 36–84 months was not effective in 29 low birth weight children who had GH deficiency. In addition, Coutant *et al.* [27] found that an average dose of 0.13 mg/kg/week had a limited effect on adult height in 70 children who were SGA and had GH deficiency. In both these studies, GH was given at a dose less than or equal to the replacement dose for GH deficiency. Also, treatment was started when the children's average age was above 10 years, which likely compromised the effect (Fig. 3).

Effects of discontinuation of therapy

In order to maximize the therapeutic response, GH therapy should be continuous rather than intermittent.

Figure 3 Time to achieve an increase in height of two standard deviation was approximately 2.5 years with a growth hormone dose of 0.067 mg/kg/day and approximately 5.5 years with a dose of 0.033 mg/kg/day in short children born small for gestational age



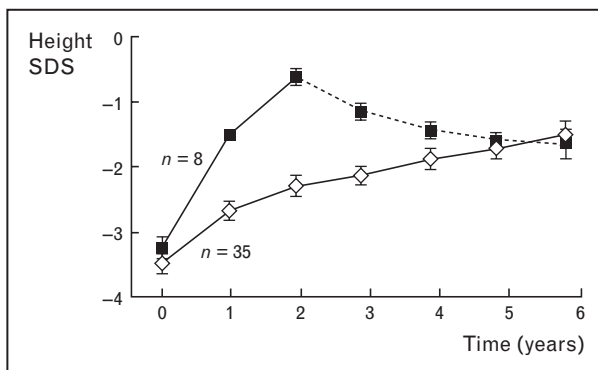
GH, growth hormone; SD, standard deviation. Reproduced from [8].

Discontinuation of treatment is always followed by a dramatic decrease in height velocity and a significantly reduced height gain, especially in the first year of observation. This catch-down growth has been observed in SGA children followed for up to 5 years after discontinuing GH therapy, leading to a mean loss of 1 SD [28]. This provides strong evidence that GH should be given in a continuous manner after normalization of height (Fig. 4).

Effects of growth hormone therapy on metabolism

Prior to starting GH therapy, fasting glucose, insulin, lipid levels, IGF-1 and IGFBP-3 levels should be measured. During the treatment, IGF-1 levels will rise in all patients who are successfully treated and will at least double from baseline levels. A steady state of IGF-1 levels is only reached after approximately 3 months from start of

Figure 4 Discontinuation of growth hormone treatment, 0.1 mg/kg/day, after 2 years leads to a reduction in height velocity and a subsequent decrease in height standard deviation compared with the sustained improvement in height achieved with a continuous dose of 0.033 mg/kg/day



GH, growth hormone; SD, standard deviation. Reproduced from [8].

therapy. The IGF-1 generation test does not add any meaningful information in this indication and therefore should not be done.

On a molar basis, the increase in IGF-1 levels exceeds that of IGFBP-3, and consequently, the molar IGF-1 to IGFBP3 ratio is significantly increased [9,23]. Pretreatment IGF-1 levels may have a role in predicting responsiveness to GH [29], whereas in children receiving GH, monitoring of IGF-1 levels as a tool for dose optimization may be useful. In all other aspects, standard monitoring of GH therapy should be applied in terms of routine measurements of thyroid hormone levels, glycosylated hemoglobin A1C (HbA1C) and glucose [30].

GH therapy in SGA children also improves body composition, blood pressure (BP) and lipid metabolism as shown in a study of 79 SGA patients. Before GH therapy, BMI SD was significantly lower than zero but increased significantly to higher values during therapy with GH [31]. This progressive normalization was not accompanied by an overall change in the percentage of body fat but rather a change in muscle mass. Similarly, Leger *et al.* [32] studied the long-term effects on muscle and adipose tissue in 14 short children born SGA during 3 years of GH therapy and one-year withdrawal period. By the end of the third year, muscle mass remained significantly greater in the SGA group than in the control group, but the two groups had similar adipose tissue mass.

Pharmacogenetic effects of growth hormone therapy in small for gestational age children

A common genetic variant in the GH receptor that is associated with variation in the GH response in children born SGA and in those with idiopathic short stature has been described [33]. Children carrying an exon 3 deletion of the GH receptor demonstrated 1.7–2 times more growth acceleration induced by GH than children with the full-length variant of the GH receptor. This finding was recently confirmed by another group of investigators in GH-deficient children both in their initial growth response and in their adult height achieved after GH therapy [34]. If these variations would confer an increased or diminished sensitivity to GH, one would also expect height differences in the normal population based on GH receptor status. Nonetheless, these studies may eventually lead to genetic testing that could contribute to individualized and more effective GH therapy much like IGF-1-based dosing of GH therapy proposed by other groups [35].

Safety of growth hormone therapy

GH therapy has been found to be well tolerated and highly effective in promoting growth in those former SGA infants who do not show catch-up growth by 2 years of age

[36]. Bone age has been shown to be normal or delayed in individuals born SGA. Dutch workers have shown that GH treatment is associated with an acceleration of bone maturation regardless of the GH dose given [9,37]. Even in untreated infants born SGA, bone age occasionally advances by more than 1 year in a single calendar year. Furthermore, bone age is a poor predictor of pubertal timing and adult height in children born SGA. The assessment of bone age is not recommended during routine follow-up.

The effect of GH on glucose metabolism in children born SGA is of potential concern, and carbohydrate metabolism should be assessed at baseline and thereafter repeatedly every year during GH therapy. Insulin resistance is not an unexpected finding in short children born SGA [38] and subsequently in adults born SGA [5]. Although 8% of 8-year-old children had an abnormal glucose tolerance test, none developed diabetes mellitus over the subsequent 10 years [39]. As per the International SGA Advisory Board, the majority of prepubertal children who are SGA are not at risk for glucose intolerance. Parents should be asked about a family history of type 2 diabetes as GH therapy can cause an increase in insulin resistance. It is more evident in prepubertal children who show rapid weight gain and a BMI above 17 kg/m² [40–42]. (Fig. 5)

Insulin resistance may increase during GH therapy in SGA children as described in short appropriate for gestational age (AGA) children receiving GH [43]. Fasting serum glucose and insulin levels should be measured annually. No adverse effects on serum glucose and HbA1C levels were found in 78 prepubertal children who were treated continuously with GH at a dose of either 0.24 or 0.48 mg/kg/week for 6 years [39]. Blüher

et al. [44] studied the relationship between insulin resistance and plasma concentration of tumor necrosis factor alpha, angiotensin II, GH and IGF-1, which are potential modulators of the insulin signaling pathway. None of these factors was elevated in obese individuals who had impaired glucose tolerance and were at an early stage of development of diabetes. This suggests that elevation of GH or IGF-1 is not a primary metabolic abnormality leading to insulin resistance. In lean children without a family history of diabetes, screening of the carbohydrate status with fasting and postprandial glucose levels is suitable. More stringent measures are recommended for those who are at puberty, are obese or have other risk factors (Fig. 6) [45].

In a recent US GH trial in children born SGA, although insulin and HbA1C levels as well as homeostasis model assessment (HOMA) and quantitative insulin-sensitivity check index (QUICKI) scores rose slightly, these changes were not clinically significant [36]. Reassuringly, the changes in carbohydrate metabolism appear to be largely reversible when GH treatment is terminated [39,46]. However, the long-term risks of sustained GH therapy in children born SGA have not been determined.

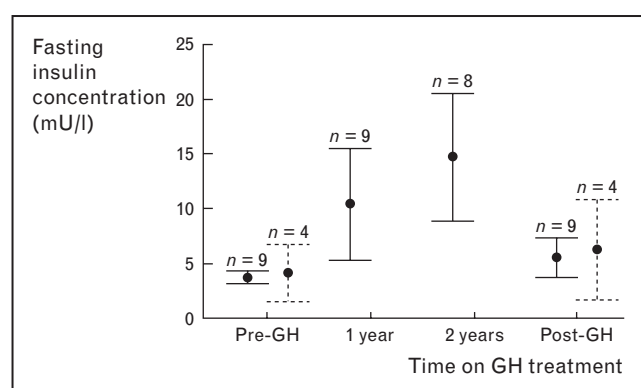
Short children born SGA are at increased risk of hyperlipidemia [47], and children born SGA are at increased risk for hypertension [31,48], therefore, plasma lipid levels and BP should be measured prior to GH therapy. There is a small effect of SGA on BP, primarily systolic, but no increased risk of childhood or adolescent hypertension. Although in well established cohorts there is evidence of tracking of metabolic risk factors from childhood to adulthood, there are no such data specifically for SGA children. Obesity and accelerated weight gain are likely to be the major risk factors [49].

Children born SGA may also have an inherent risk of cardiovascular disease and dyslipidemia in later life [47,49]. Reassuringly, a study of children born SGA treated with GH showed that those who had elevated systolic BP before treatment had a reduction in BP over time [31]. Furthermore, total cholesterol and low-density lipoprotein levels fell during the first year of treatment and remained stable thereafter [31,46].

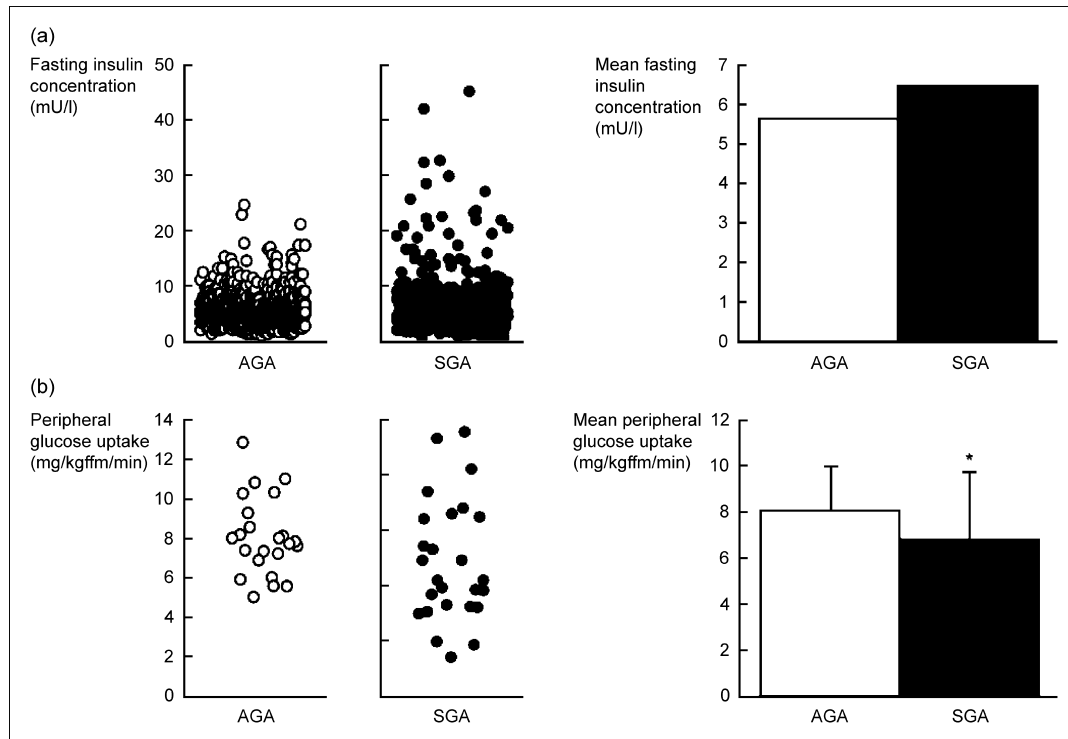
As expected, bone age advances more than 1 year per treatment year [37]. This is also seen in other GH treatment studies during catch-up growth.

Postmarketing surveillance has so far shown that GH therapy is well tolerated. Importantly, there is no evidence that the risk of malignancy is increased [36]. As in other children treated with GH, benign intracranial hypertension is a rare complication of treatment in SGA children, occurring in approximately one in 1000

Figure 5 Fasting insulin concentrations (mean and 95% confidence intervals) in untreated short children born small for gestational age and in those receiving growth hormone therapy at a dose of 100 g/kg/day for up to 2 years



GH, growth hormone. Reproduced from [23].

Figure 6 Insulin resistance in the Haguenau study of individuals born small for gestational age

(a) Fasting insulin concentrations in 734 adults born and 689 born appropriate for gestational age. (b) Peripheral glucose uptake during hyperinsulinemic clamps in 26 individuals born small for gestational age and 25 born appropriate for gestational age. The left-hand graphs represent individual values and the right-hand graphs represent the mean values observed in the two groups. Black circles and bars, SGA; open circles and bars, AGA. AGA, appropriate for gestational age; kgffm, kilograms fat-free mass; SGA, small for gestational age. * $P = 0.05$ compared with individuals born AGA. Reproduced with permission from [45].

individuals. There is convincing epidemiological evidence that children born SGA, even those not treated with GH, may be at an increased risk of insulin resistance and diabetes mellitus later in life [5,38]. These inherent risks of obesity and insulin resistance later appear to be greatest among those children born SGA who show spontaneous catch-up growth rather than among the population of short children born SGA who would qualify for GH therapy [1,50,51].

Conclusion

Birth size and early postnatal growth appear to influence the onset of several endocrine and metabolic disorders of childhood. The incidence of SGA is now 2.3–10% of all live births. Approximately 10% of children born SGA will not achieve catch-up growth and will remain -2 SD or less for height throughout childhood and adolescence into adulthood.

Although there are several endocrine and metabolic disturbances associated with SGA infants, there is currently no strong evidence to recommend routine endocrine evaluation in infants born SGA [52*,53*]. GH therapy is indicated in children born SGA who do

not achieve catch-up growth by 2–3 years of age. The use of GH in children born SGA has been found to be well tolerated and efficacious and is an important advance in the treatment of short stature in pediatrics.

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