

**CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA):  
A NEW FRONTIER FOR GH THERAPY**

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**Abstract**

A 9 member independent panel of endocrinologists and pediatricians was convened to discuss basic issues with respect to definition, diagnosis, and clinical management of children born small for gestational age (SGA). SGA is defined as the situation when birth weight and/or length are at least 2 standard deviations (SD-s) below the mean for gestational age (<2 SD). The seven consensus guidelines agreed by the panel members are as follows:

i. Children born SGA have a serious and permanent handicap of growth in adulthood if not treated.

ii. Any term newborn lighter than 2500 g (male) or 2000 g (female) may be considered SGA.

iii. When 4 years of age, all children born SGA will be evaluated for height, height velocity, bone age. Preterm children and multiples should be included even if they were AGA. All children having concomitantly a SD score of < -2.5, a HVSD score < -1 and a bone age (Greulich-Pyle) smaller or equal to the chronological age are to be considered candidates to GH therapy.

iv. All recognizable short stature syndromes must be extracted from the contingent of SGA by clinical and laboratory thorough evaluation and subjected to their distinctive growth disturbance protocol.

v. The rest of candidates will receive GH therapy at 0.35 mg/kg/week daily dosage. A biochemical screening including hormonal and IGF I determinations and also hematology should be performed before administering the first injection. GH dynamic tests are not recommended as a rule.

vi. Effectiveness of the therapy will be appreciated after 6-12 months of uninterrupted therapy. Annualized growth rates higher than 7 cm/yr are considered proofs in favor of successful therapy. IGF I levels higher than 600 ng/ml should be avoided.

vii. After the inclusion in therapy and the first evaluation, the patients follow-up should align to the standard provisions of the national or regional programs of GH therapy.

**Key words:** small for gestational age, intrauterine growth retardation, catch-up growth, short stature, growth hormone therapy.

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## INTRODUCTION

The World Health Organization has defined low birth weight as a weight of less than 2500 g (WHO- (1). The term “small for gestational age” (SGA) is used to describe fetuses or newborn infants whose weight and length is less than expected for their gestational age and sex (2,3). Most of children born SGA achieve an appropriate catch-up growth by 2 or 3 years of age. Some of them (10-15%) do not catch up and experience growth delay during entire childhood. The definition of SGA is arbitrary, but in growth clinics SGA is commonly defined as birth weight and/or length two or more standard deviation scores below the mean for gender and gestation ( $-2$  standard deviations, SD-s), which is consistent with the definition of childhood short stature (standing height  $<2$  SD-s). As birth length is not always available in Romania and is often not as reliably measured as weight, SGA is customarily defined in many countries by birth weight alone.

Being born SGA carries an elevated risk of developing metabolic disease in later life, particularly obesity, insulin resistance, carbohydrate intolerance, and dyslipidemia. Poor maternal nutrition seems to be the main cause of such troubles, especially for insulin resistance and tendency to diabetes. There is an intriguing relationship between the rate of recovery of weight and pathology in later life. So, according to (4), subjects born SGA who gain weight excessively during childhood have a poor prognosis for developing coronary heart disease late in adult life. Moreover, growing rapidly in the first two years of life exposes any subject, born SGA or AGA (adequate for gestational age), to the risk of hypertension and obesity even earlier, in the third decade of life. In conclusion, being born SGA confers a substantial risk of morbidity in adulthood, apart from the psychological and discriminative consequences of the short stature in itself. At the same time, the consequences of the rapid gain of various parameters in early postnatal years stress that inducing the catch-up too early by, say, growth hormone therapy or other means may be wrong for the organism economy.

## DEFINITION AND NATURAL HISTORY

Neonates with either low birth weight or length or both for gestational age should be considered SGA. “Low” birth weight or length seems more than 2 SD-s under the mean for the reference data. Accordingly, subject to available data, it is very useful to learn that those who are born SGA may be further classified as SGAW (low birth weight), SGAL (low birth length), or SGAWL (low birth weight and length), just because there are differences in their response to GH therapy. So, it is crystal clear that the term “SGA” refers only to the size at birth and nothing else. The term “intrauterine growth retardation” (IUGR) suggests diminished growth velocity in the fetus as documented by at least 2 intrauterine growth assessments (5). SGA and IUGR are not synonymous. IUGR indicates the presence of a pathophysiologic process occurring *in utero* that inhibits fetal growth. A child who is born SGA has not necessarily suffered from IUGR, and infants who are born after a short period of IUGR are not necessarily

SGA. These are important elements for defining but ultimately all depends on the accuracy or even of the very existence of the appropriate reference data for birth weight and birth length available for the population, and country- or ethnic-specific normative data are important for identifying those at risk. In the United States, for instance, the most commonly used data on intrauterine growth come from charts developed by Usher and McLean (2). However, such data do not exist in many countries, including Romania and efforts should be made to improve the existing regional reference data to become nationwide. For the time being, adequate nationwide standards for birth weight and length are not available. We propose the provisional cutoff at term (38 weeks) for weight 2500 g in male and 2000 g in female. For these reasons, the accuracy of birth weight and birth length measurements and, particularly, of gestational dating is crucial. Generally, there are two situations in which defining a child as SGA is difficult: i. lack of gestational (precise) data and ii. some very premature (gestational age <30 weeks) infants who are AGA and have very low birth weight may exhibit early postnatal growth failure. Multiplets are close to the latter situation.

A recent study of 3650 term singleton SGA infants (6) showed that postnatal growth acceleration, or catch-up growth, results in approximately 87% SGA children being within the normal population height standards (2 SDS) by 2 years of age (1). The mean final height in the subjects with catch-up growth was  $-0.7$  SDS compared with  $-1.7$  SDS in those who had not caught up by 2 years. At 18 years of age, 7.9% of the subjects born SGA remained short; in spite of the fact that a minority (5%) continued to catch up spontaneously during childhood. The best predictors of catch-up growth were longer birth length and taller midparental height. A significant number of SGA infants are born prematurely; they have a different pattern of postnatal growth where catch-up growth occurs at a later age than term SGA infants (7, 8). In the Dutch study, referred there (7, Table 1), there was no significant difference in the proportion of term and preterm SGA children who had caught up at 2 years, but at 6 months and 1 year fewer premature SGA children had catch-up growth. Thus, determining exactly the gestational age of any low birth weight child is important during any assessment of their early postnatal growth, to avoid wrongly assigning a premature infant, in fact a delayed catch-up grower, to a non-catch-up group.

It is therefore appropriate that the GH therapy European licence for short SGA children recommends that treatment should not be commenced before the age of 4 years. We must wait sufficiently to avoid deleterious consequences in later life. In addition it is recommended that the height velocity SD score should be below average to reduce the possibility of treating any SGA child with spontaneous catch-up growth.

Catch-up growth in short children who are born SGA has been defined in a number of ways. A general definition is growth velocity (cm/y) greater than the mean for chronological age and gender (9). For practical reasons, definition of a successful catch-up growth is based on the greater than  $-2$  height SD score for the children at 4 years of age (or above the third percentile). Such a simple definition does not incorporate the patient's **expected adult height** based on parental stature (target height) commonly estimated by the midparental height corrected for gender (9). Target

height -that is, an estimate of genetic potential in stature - is a strong predictor of response to GH therapy (10).

Most children who are born SGA experience catch-up growth and will achieve a height closer than -2 SD to the mean. Catch-up is typically an early postnatal process that in most SGA infants is completed by the age of 2 years (11,12), but not in all. Premature SGA infants (<37 weeks' gestation) may take longer to catch up than full-term SGA infants. In 80% of infants who are born SGA, catch-up growth occurs during the first 6 months of life (13). Approximately 10% of children born SGA will remain at more than -2 SDs under the mean for height throughout childhood and adolescence and into adulthood (13,14). Among children who are born SGA and do not achieve catch-up by 2 years of age, the relative risk of short stature (-2 SD) at 18 years of age is 5.2% for those with low birth weight and 7.1% for those with low birth length (12). Therefore, a short child who was born SGA and has not caught up by 2 to 3 years of age and whose catch-up growth has stopped should be referred to those having expertise in endocrinology.

## **HORMONAL REGULATION OF (CATCH-UP) GROWTH IN SGA CHILDREN**

As said above, immediately after birth most children begin to grow actively. The endocrine mechanisms governing catch-up growth are still poorly understood, although (4) proposed that they reside within the growth plate and are based on a delay in normal growth plate senescence.

### **1. Growth Hormone**

Infants born SGA frequently exhibit increased concentrations of GH (15-17) and have low levels of IGF-I and IGFBP-3, suggesting that SGA neonates are GH insensitive.

Normalization of the GH-IGF axis occurs early in postnatal life (18), and most children born SGA go on to show a normal response to GH stimulation testing and have normal levels of IGF-I and IGFBP-3 (19). Disturbances in GH dynamics are similar to what is seen in adults with long-term critical illness (20), and it has been suggested that altered GH secretion at birth may represent a consequence of extended critical illness *in utero* (21).

### **2. The IGF system**

Decreased levels of IGF-I have been detected in fetuses and infants born SGA, indicating that dysfunction of IGF-I or its metabolism may be involved (18,22). Polymorphisms of IGF-I gene (23). and mutations of the IGF-IR gene (24) were described in SGA born. Despite substantial evidence of abnormal IGF levels in infants born SGA, there does not appear to be a firm link between IGF-related variables at birth and postnatal growth (15,18). It was suggested (25) that the affinity of IGFBPs for IGFs may be modulated by proteolytic enzymes that degrade the IGFBPs, thereby increasing the level and bioavailability of IGF-I. Postnatally, the

IGF system is switched on, allowing catch-up growth in the majority of infants born SGA (25). Anyway, the alterations in IGF-I levels observed in neonates born SGA appear to be transient, because they disappear soon (26). *However, serum levels of IGF-I remain significantly reduced in infants who fail to show catch-up growth and remain so in adulthood* when may be implicated in the significant association with cardiovascular and metabolic diseases .

### 3. Insulin resistance

Individuals born SGA show moderate insulin resistance in infancy, typically in the catch-up growth period from 0 to 2 yr of age (27, 28). It is interesting to note that in the study (27), insulin resistance was found only in infants born SGA who achieved catch-up growth and not in infants born SGA who did not achieve catch-up growth or who were born AGA, suggesting yet again that rapid catch-up growth can give rise to adverse metabolic outcomes. This phenomenon is further supported by a study in prepubertal children born SGA, where significant insulin resistance was found only in children with catch-up growth resulting in a current BMI of 17 kg/m<sup>2</sup> or greater (29). Insulin resistance may extend during childhood, adolescence and adulthood, as well as type 2 diabetes mellitus.

### 4. Premature adrenarche and puberty

The ages at pubertal onset and at menarche are advanced by about 5-10 months (30-32). In a Swedish study of children born SGA, there was a tendency to start puberty early, especially if catch-up growth had not occurred in early childhood (6). Several other groups, however, have not been able to show earlier puberty or menarche in children born SGA (33-36). The sequence and tempo of puberty appear to be normal. Extensive studies documented premature or exaggerated adrenarche in many children with a history of SGA (37). Low birth weight is a common risk factor for testicular cancer, hypospadias, and cryptorchidism (40).

## **CONSEQUENCES OF BEING BORN SGA**

i. increased risk of morbidity and mortality in the perinatal period: hypotension, hypoglycemia, necrotizing enterocolitis, and neonatal death (41,42).

ii. neurological impairment, delayed cognitive development, and poor academic achievement (43,44).

iii. adult cardiovascular complications, obstructive pulmonary disease, type 2 diabetes mellitus, renal insufficiency, and impaired reproductive function (45).

iv. failure to achieve appropriate catch-up growth after SGA birth results in persistent short stature and is associated with greater health risks and psychosocial impairment, compared with patients born SGA who achieve their growth potential (46).

v. Neuro - developmental, psychosocial, and behavioral outcomes are present in the medical history of many SGA born children, especially in those who did not catch-up growth. Impaired learning and cognition (47) was found in many of them.

## CAUSES OF BEING BORN SGA

### **Fetal factors**

*Chromosomal abnormalities* of number or structure (Down syndrome, Turner syndrome, autosomal aberrations and others);

*Genic diseases* (achondroplasia and other chondrodysplasias);

*Congenital anomalies* (e.g. cardiac malformations);

### **Maternal factors**

*Medical conditions* (hypertension, renal disease, diabetes mellitus - advanced stages, systemic lupus erythematosus);

*Maternal hypoxemia* (cyanotic heart disease, chronic anemia, chronic pulmonary disease);

Infection (toxoplasmosis, rubella, cytomegalovirus, herpes virus, human immunodeficiency virus);

*Nutritional disturbances* (low pre pregnancy weight, poor weight gain during pregnancy, substance use/abuse, cigarette smoking, alcohol illicit drugs, therapeutic drugs as warfarin, anticonvulsants, antineoplastic agents, folic acid antagonists);

*Uterine/placental factors* (single umbilical artery, velamentous umbilical cord insertion, placental malpositions and malformations);

*Demographic factors* (maternal age, height, weight, race, parity, history, previous delivery of SGA infants, multiple gestation);

Adapted and shortened after many well-known authors cited by (48).

## TREATING A SHORT CHILD BORN SGA

A short child who was born SGA and has not caught-up (*i.e.* - 2 SDs below the mean) by 4 yr of age and who is growing at a subnormal rate for age could become a candidate for GH therapy (13,14). In addition to the above criteria, treatment with GH is indicated only when other causes of short stature, such as growth-inhibiting medication, chronic disease, endocrine disorders such as hypothyroidism, emotional deprivation, or syndromes associated with poor growth have been ruled out (49).

GH secretion testing does not provide clinically useful information for the routine treatment of short children who were born SGA. Arguments that favor evaluation for GH deficiency stem from data suggesting that many short patients who were born SGA have diminished secretion of GH. The present recommendation is that tests of adequate GH release should be performed only when GH deficiency is suspected. However, the measurement of circulating concentrations of IGF-I and, whenever possible, of IGFBP-3 before the start of GH therapy is strongly advisable in all children in whom a decision to treat was taken. These measurements not only provide a baseline against which to assess the biochemical response to GH therapy, but also serve as a useful screen for possible

GH deficiency in this population. As would be expected, GH therapy in short children born SGA provokes a dose-related rise in the serum concentrations of both IGF-I and IGFBP-3 from low to high levels, but the rise is difficult to quantify.

Although specific recommendations regarding an optimal treatment regimen must await additional investigation, published studies showed that GH therapy is effective and safe for persistently short children who were born SGA and achieved insufficient catch-up growth. A number of clinical trials have confirmed that GH effectively and safely induces catch-up growth in short prepubertal children who were born SGA. Although the increment in adult height resulting from GH treatment is not yet precisely defined, most trials reported to date demonstrate stimulation of skeletal growth of sufficient duration and magnitude to recommend therapy.

Long-term continuous GH therapy at a dose of 0.24 mg/kg/wk (for those GH deficient) or 0.48 mg/kg/wk (for those not GH deficient) in short children who were born SGA results in normalization of height and subsequent growth along the target height percentile. The 5-year increase in height SD score for chronologic age was  $2.6 \pm 0.9$  for the 0.48 mg group and  $2.2 \pm 0.6$  for the 0.24 mg group; these changes were significantly different from baseline values ( $P < 0.001$ ), but not significantly different from each other. Also, this 5-year increase did not differ between those with GH deficiency and those without GH deficiency but the dosages differed. No drug-related adverse events were reported.

In July 2001, GH was approved by the US Food and Drug Administration for the long-term treatment of growth failure in children who are born SGA and do not achieve catch-up growth by 2 years of age, at dosages up to 0.48 mg/kg/wk.

The recent approval (50) of recombinant human growth hormone (rhGH) for the treatment of short stature in SGA children by the European Union's Committee on Proprietary Medicinal Products offers a new licensed therapeutic option. Reference to selection of patients, effectiveness, safety, and its potential metabolic implications mark some differences vs the American licensing. The dosage recommendation (0.25 mg/kg/week) and the age cutoff chosen (4 years) are the most important at the first glance.

The Romanian experience in treating short children born SGA is scarce. Dosage necessary to get a growth rate higher than 7 cm/yr seems to be closer to 0.48 than 0.24 mg/kg/week (M. Popa, unpublished data). Credible data on the epidemiology of persistent shortness in SGA children are also lacking, as well as the expertise in currently monitoring the therapy by IGF I determinations. The Romanian Advisory Committee on GH Therapy in Children Born SGA was founded in May 2007 by 9 specialists who participated in the Annual Meeting of the Romanian Society of Psychoneuroendocrinology. In its first session, the Committee adopted unanimously the following memento for all specialists who are to use GH for children born SGA. The memento is formulated as a heptalogue.

i. Children born SGA may have a serious and permanent handicap of growth in adulthood if they are not treated.

ii. Any term newborn lighter than 2500 g (male) or 2000 g (female) may be considered small for gestational age.

iii. When 4 years of age, all children born SGA will be evaluated for height, height velocity, bone age. Preterm children and multiples should be included even if they were AGA. All children having concomitantly a SD score of  $< -2.5$ , a HVSD score  $< -1$  according to the standards of Prader *et al* (1988) and a bone age (Greulich-Pyle) smaller or equal to the chronological age are to be considered candidates to GH therapy.

iv. All recognizable short stature syndromes must be extracted from the contingent of SGA by clinical and laboratory thorough evaluation and subjected to their distinctive growth disturbance protocol, if the case.

v. The rest of candidates will receive GH therapy at 0.35 mg/kg/week dosage given daily. A biochemical screening including hormonal and IGF I determinations and also hematology should be performed before administering the first injection. GH dynamic tests are not recommended as a rule.

vi. Effectiveness of the therapy will be appreciated after 6-12 months of uninterrupted therapy. Annualized growth rates higher than 7 cm/yr are considered proofs in favor of successful therapy. IGF I levels higher than 600 ng/ml should be avoided.

vii. After the inclusion in therapy and the first evaluation, the patients follow-up should align to the standard provisions of the national or regional programs of GH therapy.

## CONCLUSIONS

Short SGA children should first be investigated in order to identify causes of being born SGA and reasons for poor postnatal growth. The child must have clearly demonstrated that there has been no spontaneous catch-up growth. In other words there must be short stature (height SDS  $-2.5$ ), age 4 years or over, and height velocity below average. Any specific cause found should be treated appropriately. In the child that then remains short or in whom no remediable cause has been identified, GH therapy may have a role to play in normalizing height, and the more precisely the child is identified, the greater will be the potential response to treatment. Determination of the GH status is not necessary but pretreatment IGF-I, IGF-BP3, fasting insulin, glucose, and lipids should be determined and blood pressure measured. Treatment should be started after clinical assessment by an endocrinologist and should follow the same technical rules of care currently used for other GH indications. The initial dose recommended of 0.35 mg/kg/week appears to be adequate for any age. Adjustment of the dosage must be performed in the first 6-12 months of therapy.

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Small for gestational age (SGA) refers to an infant born with a birth weight less than the 10th centile. Severe SGA refers to an infant born with a birth weight less than the 3rd centile[1]. They fall into three groups: Babies whose growth at all gestational ages has been low. They are SGA but otherwise healthy. 50-70% of SGA fetuses are constitutionally small, with fetal growth appropriate for maternal size and ethnicity[1]. Growth is normal in the early part of pregnancy but slows in utero by at least two measurements (normally from ultrasound assessments).  
Antithrombotic therapy appears to be a promising therapy for preventing delivery of an SGA infant in high-risk women. However, there is insufficient evidence, especially concerning serious adverse effects, to recommend its use. Morbidity. Primary prevention of children being born small for gestational age (SGA) and intrauterine growth restriction (IUGR) should target the main etiology and mechanisms, which in developed countries are smoking, alcohol, infection, and preeclampsia as major causes of decreased placental flow. View.  
Background A legitimate indication for growth hormone (GH) therapy in children born too light or short at birth [small-for-gestational age (SGA)] exists in Germany and the European Union only if special criteria are met. Methods We conducted a longitudinal, multi-centered study on full-term appropriate-for-gestational age (AGA, n=1496) and pre-term born SGA (n=173) and full-term SGA children (n=891) in Germany from 2006 to 2010. New articles related to this author's research. Email address for updates. Done. My profile My library Metrics Alerts.  
Children born small for gestational age (SGA): a new frontier for GH therapy. M Popa. ACTA ENDOCRINOLOGICA-BUCHAREST- 3 (3), 371, 2007.