Children Born Small for Gestational Age: Growth Patterns, Growth Hormone Treatment and Long-Term Sequelae

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The endocrine system, in particular growth hormone and thyroid hormones, plays an important role in postnatal growth, whereas intrauterine growth is almost independent of fetal pituitary hormones. Insulin and insulin-like growth factors exert a major effect on fetal growth and size at birth. Insulin stimulates accumulation of adipose tissue, induces protein synthesis and hepatic glycogen storage, and enables the release of different growth factors from fetal tissues. IGF-1 and IGF-II, which in the fetus function independently of pituitary GH, exert important effects on the growth and differentiation of tissues. The placental lactogen, which has GH-like action, also seems to be a contributory factor in fetal growth.

Normal intrauterine growth depends on the genetic potential and is influenced by hormonal and environmental factors, including maternal nutrition and health. The term intrauterine growth retardation and small for gestational age are not synonymous. IUGR is defined as restriction of fetal growth, whereas SGA refers to an infant born with a weight or length that is 2 SD below the mean for his or her gestational age. SGA is related to an increased risk of perinatal morbidity and mortality, developmental disabilities, and a tendency to reduced postnatal growth with final short stature. Clinical research has indicated that SGA may have a long-term impact on metabolic factors, such as increased incidence of hypertension, cardiovascular disease, lipid disorders, impaired glucose tolerance and type 2 diabetes. In this review, we focus on the known etiologies of SGA, growth patterns, potential benefits of growth hormone treatment in these patients, and long-term sequelae of SGA.

Definition of IUGR/SGA

There are three phases of fetal growth: the phase of cell hyperplasia during the first 16 weeks of gestation, the phase of hyperplasia and hypertrophy during 16–32 gestational weeks, and the final phase of rapid cellular hypertrophy that occurs between 3 and 40 gestational weeks. These processes form the basis for the clinical classification of fetal growth retardation.

IUGR is diagnosed by direct intrauterine growth assessment (measurements of abdominal circumference, biparietal diameter, head circumference and skeletal length), which is evaluated by ultrasound or when the fetus length is less than 2 SD (or third percentile) below the mean for gestational age [1]. IUGR is classified as reduced growth that is symmetric or asymmetric. In symmetric IUGR all fetal organs are decreased proportionately, and the process occurs early during gestation, whereas asymmetric IUGR is a later process with relatively greater decrease in abdominal size (liver volume and subcutaneous tissue) than head circumference. Asymmetric IUGR is more common and may be attributed to the capacity of the fetus to adapt to a hostile environment by redistributing blood flow to the vital structures – brain, heart and placenta – at the expense of the abdominal viscera.

When the newborn body size (weight or length) is inappropriate for gestational age it is referred to as SGA. Since both fetal weight and length gains are closely related, there is much overlap between IUGR and SGA. There is no generally accepted standard definition for SGA. Commonly used definitions of SGA are: birth weight less than the 5th or 10th percentile for gestational age [2]; birth weight less than 2 SD below the mean value for gestational age; and birth weight less than 2,500 g at gestational age greater than or equal to 37 weeks [3]. As short stature in later life is usually defined as a height below 2 SD of a reference population, it seems more appropriate to define SGA in terms of short length at birth, i.e., a birth length below 2 SD for gestational age. However, many nurseries record birth weight and not birth length at delivery.

Etiology of IUGR

Several factors play an important role in the pathogenesis of IUGR. Fetal growth failure may be due to extrinsic factors, mainly maternal disorders and placental abnormalities, or intrinsic growth retardation from dysfunction in the fetus [4]. However, the biochemical and cellular basis for abnormal fetal growth in most cases of IUGR remains unclear. Although infants with IUGR due to extrinsic factors have a better growth potential than those with IUGR due to intrinsic factors, postnatal growth is not always normal.

Extrinsic factors

The extrinsic factors occur as a result of placental disorders or maternal disease that compromise the delivery of oxygen and nutrients to the fetus. The decreased rate of fetal growth seems to be the result of adaptation to an inadequate nutrient supply during gestation.

IGF = insulin-like growth factor
GH = growth hormone
IUGR = intrauterine growth retardation
SGA = small for gestational age

- *Placental abnormalities* include abnormal implantation of the placenta, placental vascular insufficiency and vascular malformations.
- *Maternal disorders* include impaired nutritional status. Chronic malnutrition or starvation is responsible for a large proportion of infants with IUGR.

Early fetal malnutrition may affect growth permanently by reducing cell proliferation and size. In later gestational stages, malnutrition will result in preservation of cells with decrease in their size, which might also result in growth deficit. Maternal malnutrition may have an impact not only on the fetus size but also on growth during the first year of life [5]. Uterine malformations and constraints on uterine growth can cause IUGR. Maternal illness is another contributing factor – such as hypertension, toxemia, systemic hypoxemia, which are found in mothers with cardiac disease, uncontrolled diabetes mellitus, renal disease, severe asthma or severe anemia. Additional maternal risk factors associated with IUGR include maternal short stature, short interval between pregnancies, multiple pregnancies with limited fetal growth, and substance abuse [6], tobacco smoking [7] and alcohol ingestion [8]. The mechanisms for such drug-induced fetal growth retardation are unclear but probably include uterine vasoconstriction and vascular insufficiency.

Intrinsic factors

Intrinsic fetal factors that tend to be related to IUGR include:

- *Chromosomal disorders* such as Down syndrome, Turner syndrome, trisomies 13 and 18 [9].
- *Syndromes associated with congenital malformations and primary growth failure* such as Russell-Silver, Seckel, Noonan**,** Cockayne, Bloom, Prader-Willi, Rubinstein-Taybi and progeria.
- *Fetal infections* are usually responsible for early onset of IUGR. They include the TORCH syndrome: **to**xoplasmosis, tuberculosis, **r**ubella, **c**ytomegalovirus, **h**erpes simplex, as well as human immunodeficiency virus, syphilis and others. These viruses reduce birth weight by inhibiting cell division and inducing cell death [10].
- *Primary abnormalities of the GH-IGF-1 axis* have been reported in infants with IUGR [11]. There is evidence that GH, IGF-1 and IGF-binding protein 3 are regulated differently in SGA infants compared to infants with a weight appropriate for gestational age [11]. Documentation of birth size of newborns with mutations of the *GH* or *GH*-receptor gene has indicated that fetal GH makes a small but significant contribution to birth size. Gene knockout studies have shown that elimination of production of IGF-1 has a major impact on fetal and postnatal growth. The reported case of an IGF-1 gene deletion had the same growth characteristics as observed in the murine IGF-1 knockout presenting with severe IUGR and postnatal growth retardation that was unresponsive to GH treatment [12]. Thus, although the fetus may be GH-independent, the local tissue production of IGF-1 is critical for normal intrauterine growth, and indeed a positive correlation between the serum levels of IGF-1 and birth weight has been reported [13]. It was also reported that the cord levels of IGF-1 and IGF-II are lower in SGA infants compared to appropriate for gestational age infants [14]. Job et al. [15] reported that SGA infants have higher basal and stimulated levels of serum GH, which might indicate GH resistance.

Catch-up growth in SGA infants

Nearly 3% of human infants are born small for gestational age. Postnatal weight gain varies widely in these infants, but most SGA infants show good postnatal catch-up growth. This occurs when the postnatal environment provides sufficient nutritional support during the first 2 years of life, with most infants achieving this growth in the first 6 months [16]. Catch-up growth is usually defined as accelerated growth to a height above the third or fifth percentile [3]. Spontaneous catch-up growth usually starts early after birth, proceeds over 2 years or less, and ends at a growth level that subsequently remains stable throughout the childhood years [16,17].

Approximately 10–15% of SGA children fail to achieve sufficient catch-up growth that will bring them into the normal height range throughout childhood. They present with a height deficit during childhood that in almost all cases results in short adult stature [17]. The pathophysiologic mechanisms underlying the insufficient spontaneous catch-up growth in children with short stature born SGA remain obscure.

The infancy-childhood-puberty growth model, developed by Karlberg et al. [18], was based on the observation of normal infants' growth. This model divides the growth process into three overlapping phases. The infancy phase begins at mid-gestation and ends at about 3 years of age and represents the postnatal continuation of fetal growth. The childhood phase begins between 6 and 12 months of age and continues with a steady growth velocity into puberty. The pubertal phase is characterized by the pubertal growth spurt, followed by a deceleration of growth until attainment of final adult height.

Although GH and GH receptors are present during fetal life, the growth-promoting action of GH begins between 6 and 12 months of age, when an increase in serum IGF-1 levels is accompanied by an increase in length velocity. According to the infancy-childhood-puberty growth model, fetal growth regulatory forces continue postnatally as the main linear growth factors up to 6 months of age. Thus, it is proposed that length or weight at 6 months represents a more accurate estimation of fetal growth than birth size.

The catch-up in length of SGA usually occurs during the first 3–6 months of life, suggesting that these infants suffered from a disturbed fetal environment followed by normal growth when the environmental condition improved. Infants who fail to catch-up can be defined more accurately at 6 months of age. This group may suffer from a malfunction of the fetal growth regulatory process, which depends on genetic factors. After this age, low growth rate could be attributed to difficulties in the transition to the GH regulatory phase or malfunction of the GH-IGF-I axis.

Some studies sought the predicting factors for catch-up growth. According to Leger et al. [19], the most important factors determining the final height in SGA children are parental height, especially the mother's stature and birth length, rather than gender

or birth weight. Hokken-Koelega et al. [16] studied the postnatal growth of 724 SGA infants (423 premature, 301 full-term) in the first 2 years of life. They found that the percentage of premature SGA infants with catch-up growth at 2 years of age (82.5%) was not significantly different from that of full-term SGA infants (87.5%), but premature infants need a longer period for their catch-up. Birth length standard deviation score was more sensitive than birth weight SD score in predicting catch-up in premature SGA infants. In contrast, birth weight SD score was the best predictor for catch-up in full-term SGA infants. Gestational age, multiple birth and gender were not associated with catch-up growth at 2 years. Strauss and Dietz [20] did not find differences in terms of risk factors (birth weight and length, maternal size and weight gain, placental size, smoking, toxemia or hypertension) between SGA infants who showed catch-up growth and those who did not, suggesting that genetic factors account for the persistent effect of SGA on growth.

The postnatal catch-up growth may be related to levels of satiety and food intake. A recent study [21] examined the hypothesis that variable rates of weight gain in SGA infants are associated with variation in circulating ghrelin (the natural ligand of the GH secretagogue receptor, which has a potent orexigenic effect). In this study, SGA infants with poor catch-up growth showed a greater decline in ghrelin concentrations post-intravenous glucose compared with higher post-prandial ghrelin levels and reduced ghrelin suppression in SGA infants with good catch-up growth, suggesting that a sustained orexigenic drive contributes to postnatal catch-up growth.

Jaquet and colleagues [22] found that newborns with IUGR had significantly lower leptin levels than those with normal growth. Children born with IUGR demonstrated high serum leptin values during the first year of life [23]. It was suggested that these children develop an adaptive leptin resistance beneficial for their catch-up growth. Maor et al. [24] observed that leptin acts as a skeletal growth factor with a direct effect on skeletal growth receptor expression, and some of its effects on the bone may be mediated by the IGF system through regulation of IGF-1 receptor expression. We can speculate that the high circulating leptin levels in SGA during the first year might contribute to their catch-up growth.

There are two proposed models for the mechanisms governing catch-up growth: the neuroendocrine hypothesis and the growth plate hypothesis. The neuroendocrine hypothesis (Tanner's hypothesis) [25] involves a mechanism that is able to recognize the degree of mismatch between the target size and actual size and to adjust growth rate according to the degree of mismatch. Mosier [26] supported Tanner's model and suggested an "age-appropriate set-point for body size" located within the central nervous system that is reset to a lower level by CNS insult (head irradiation, glucocorticoid treatment). In 1994, Baron and co-workers [27] proposed the "growth plate hypothesis," based on the observation that *in vivo* suppression of growth by local administration of glucocorticoids within a single growth plate was followed by local catch-up growth. Since the catch-up was unilateral and restricted to the affected growth plate, it could not be explained by the neuroendocrine hypothesis that would have affected all growth plates.

Although genetic, ethnic and nutritional factors affect statural growth, hormonal factors – especially the somatotrophic axis and the epiphyseal growth plate – are paramount in catch-up growth. There is some evidence pointing to GH hypersecretion as a possible mechanism driving the early catch-up growth [1]. A reduction in GH secretion and low serum concentrations of IGF-1 have been reported in SGA infants [28]. It is presumed that a persistent defect in the GH-IGF-1 axis may occur in those SGA children in whom postnatal catch-up growth does not occur.

Does GH therapy have a role in the treatment of short stature due to SGA?

The possibility of improving the final adult stature of SGA children by administering recombinant human growth hormone has been the subject of debate for many years. In short children born SGA, height at the age of 2–5 years permits an estimation of the long-term height loss. However, predictions of final height based on estimations of bone age are notoriously unreliable. (There are insufficient data on the long-term benefits of rhGH-treated patients on final adult height.)

The rationale of administering rhGH to SGA infants is based on the hypothesis of a state of GH insensitivity that might be overcome by administering exogenous GH. Some children with growth failure due to SGA are also GH-deficient and these patients should be treated according to the consensus guidelines for GH-deficient patients. GH treatment in SGA children without documented GH deficiency is an indication for treatment in the United States and in some European countries, but such treatment has not been approved in Israel. Although children with SGA are not necessarily GH-deficient as defined by provocation tests, many have abnormalities in spontaneous GH secretion as well as low IGF-1 levels [28]. In addition, many short children born SGA are lean and have a lack of appetite. These children have better appetite and increased food intake after starting GH therapy [29]. GH treatment decreases serum leptin levels and body fat mass while increasing lean body mass [29], suggesting that GH therapy has a positive anabolic effect on the nutritional status of the child and thus plays an additional role in the growth of short children born SGA.

Clinical studies to date have focused on different dosage regimens and continuous versus discontinuous GH therapy [Table 1]. All these studies demonstrate that GH treatment induces acceleration in linear growth in short children born SGA. A meta-analysis of four European trials showed that the 4 year growth response was similar between continuous GH use (1 mg/m^2/day for 4 years) and discontinuous GH use (2 mg/m^2/day for 2 years, followed by 2 years without GH) [34]. These results suggest that the cumulative GH dose rather than the daily GH dose determines the growth response. de Zegher et al. [33] present an epi-analysis of 6 year growth responses obtained with GH treatment in short, non-GH-deficient SGA children. They conclude that GH administration, both continuous and discontinuous, is an effective method to normalize stature. The results of GH therapy in SGA children in this

rhGH = recombinant human growth hormone

Table 1. Comparison between various growth hormone treatment protocols for the management of IUGR

Study	**Boguszewski [30]**			**Chernausek [31]**		**Fjellestad-Paulsen [32]**		**de Zehger [33]**			
Aim	**Efficacy of different doses of GH**			**Effect of GH on linear growth**		**Effect of GH on catch-up growth**		**Continuous vs. discontinuous GH treatment**			
No. of patients	48 (18/30)			270		69		188			
(female/male)	Control	0.03	0.067	IUGR	RSS/PSS	Control	Treated	Control	Contin. 0.03	Contin. 0.067	Discont.
	12 (4/8)	16 (8/8)	20 (6/14)	144	126	31	38	49	35	27	77
Age at onset of treatment (yrs)	2–8			7.35±4.21	6.31±3.49	2–8		5.1±0.2	4.7±0.2	5.2±0.3	5.3 ±0.2
Bone age at onset of treatment				5.93±4.15	4.91±3.69	3.3±1.6	3.3±1.7				
Pubertal stage at onset of treatment	Prepubertal			Prepubertal		Prepubertal		Prepubertal			
Control	Yes			No		Yes		Yes			
GH dosage mg/kg/day	0.03 = low dose or 0.067 = intermediate dose			0.04		0.067		0.03 or 0.067			
Duration of treatment (yrs)	2			4		3		2–6			
Continuous/discontinuous protocol	Continuous			Continuous		Continuous		Continuous vs. discontinuous			
Mean height (SD score) at onset of treatment	-2.91±0.48	-3.29±0.68	-3.22±0.79	-3.49±1.16	-3.83±1.05	-3.8±0.8	-3.4±0.6	-3.2±0,2	-3.4±0.1	-4±0.3	-3.2±0.1
Height (SD score) at onset of treatment	-0.03±0.12	0.45±0.23	0.7±0.17	1.9±0.92	1.78±0.61	-1.6±1.2	-1.4±0.9				
Study population characteristics	GH sufficient without chromosomal abnormalities or chronic illnesses			Idiopathic IUGR and RSS, primordial short stature		GH sufficient without chromosomal abnormalities or chronic illnesses		GH sufficient. RSS included			
Remarks	No catch-up growth was observed in untreated group, but a clear dose-dependent growth response was found in treated group.			No change in predicted adult height. High drop-out rate – 54% of the patients.		Control group began treatment after 1 year of observation. High drop-out (32%). No difference between groups. Side effects rare, all resolved: (injection site – lipodystrophy, elevated fasting glucose, impaired glucose tolerance.		Continuous low dose and intermittent high dose are the preferred treatment.			

RSS = Russel Silver Syndrome, PSS = primordial short stature, Untr = untreated.

study are unprecedented due to the young age, the duration of treatment, the relatively large cohort, and the regimens.

The variability in growth response to GH treatment is considerable. Clinical predictors of growth response to GH treatment include chronological age and bone age at baseline [35]. The younger the child at baseline the greater the increase in height SD score for chronological age [35]. In contrast, neither the height of the parents, the pretreatment height velocity, nor the baseline bone age retardation is related to the increment in height [35]. Bone maturation is accelerated in GH-treated compared to untreated short children born SGA and healthy children [36], independently of GH dosage. The acceleration of bone maturation seen in GH-treated short patients born SGA may be due to the effects of GH treatment and/or spontaneous acceleration of bone maturation.

Some studies have reported an earlier onset of puberty in untreated short children born SGA. The question arose as to whether GH could further advance the timing of puberty and consequently reduce the growth period. Several studies have shown that mean pubertal onset was not advanced by GH treatment [35].

The average growth pattern after GH withdrawal appears to be biphasic. Initially there is catch-down followed by stabilization of height and weight at a higher level [37]. The amplitude of the catch-down during the first years after GH withdrawal appears to be independent of the previously administered GH dose [37]. It remains undetermined whether this biphasic growth pattern is primarily regulated at the neuroendocrine level or at the level of the epiphyseal growth plate.

IUGR and long-term sequelae

Intrauterine growth retardation can have adverse affects on the child's growth and development and can lead to increased morbidity and decreased longevity in the adult. The hypothesis proposed by Barker and co-workers [38] postulates that there are critical windows in fetal maturation during which inadequate

nutrition can "program" the development of adult disease. During these critical periods of rapid fetal growth, fetal compensatory mechanisms that counteract malnutrition in the short term have negative affects in the long term. Epidemiologic analyses have documented that poor growth *in utero* increases the risk of cardiovascular disease, hypertension and type 2 diabetes mellitus in adults [38]. Hales and Barker [39] proposed the "thrifty hypothesis," whereby permanent metabolic and endocrine modifications (nutritional thrift) occurring *in utero* as a result of inadequate nutrition are detrimental to the developing pancreas and thus create a predisposition for the development of type 2 diabetes. In addition, when fetal nutrition is inadequate fetal metabolic adaptations include development of tissue insulin resistance to prevent glucose metabolism in cell growth. This insulin resistance could become permanently programmed and persist in adult life, thus contributing to the development of type 2 diabetes.

The use of high doses of human growth hormone in SGA infants should take into consideration the potential risk for hyperinsulinism in infants and children with SGA and the potential side effects of growth hormone inducing insulin resistance. Therefore, concern has been expressed regarding the adverse effects of GH. Sas et al. [40] assessed the effects of long-term continuous GH treatment on body composition, blood pressure and lipid metabolism. They concluded that the body mass index normalized without overall changes in subcutaneous fat, as compared with age-matched references, whereas the blood pressure SD score and the atherogenic index decreased significantly. GH treatment was shown to have a beneficial effect on cardiovascular risk factors such as blood pressure and lipid metabolism [40].

Conclusion

Infants born small for gestational age constitute a heterogeneous group. Although most children with SGA show spontaneous catch-up growth during the first 2 years of life, approximately 10–15% fail to achieve complete catch-up growth. Studies aimed at improving linear growth by administration of exogenous growth hormone in children with SGA have shown that in some of these children GH therapy improves linear growth. The effect of GH therapy on final height is yet undetermined. IUGR has been associated with increased prevalence of diabetes mellitus type 2, hypertension and hyperlipidemia at a relatively young age in later life. Future studies need to address the effect of GH therapy on morbidity related to SGA.

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