REVIEW ARTICLE

Small for Gestational Age: Growth and Puberty Issues

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Context: Small for gestational age infants have multifold increased risk of growth failure and adulthood disorders. Those who experience rapid catch up growth are at risk of developing metabolic syndrome, whereas those without catch up may end up with short stature. These children are also prone to an altered pubertal development.

Need and Purpose: Scarcity of literature, lack of published guidelines on the follow-up and management plan of children born with small for gestational age.

Evidence Acquisition: Literature search in PubMed was conducted with regard to epidemiology, growth and puberty, comorbidities, its pathogenesis and management in small for gestational age, with particular relevance for developing countries. An algorithm for follow-up of these children is outlined, based on available empiric data.

Conclusions: Being born small for gestational age predisposes to many metabolic and pubertal disorders. Special emphasis is needed for early detection and management through early surveillance in growth clinics, and regular follow-up to prevent associated comorbidities.

Keywords: *Intrauterine Growth retardation, Puberty, Short stature*.

Being born small for gestational age (SGA), either according to weight or length, is a risk factor for growth and development disorders, and chronic diseases later in life. The term, small for gestational age' represents a statistical group of infants whose weight and/or crown-heel length is less than expected for their gestational age and sex [1]. The definition of SGA is not straightforward as it requires accurate knowledge of gestational age, measurements of birth weight, length, and head circumference, and a reference data from a relevant population. The cut-off has been variably set at the 10th centile, 3rd centile, or at less than –2 SD from the mean (approximately 2nd centile) [2]. The International Small for Gestational Age Advisory Board Consensus Development Conference Statement 2001, and the Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society 2007, recommend that SGA should be defined as a neonate whose birth weight or birth crown-heel length is at least 2 standard deviations (-2 SD) below the mean for the gestational age, based on data derived from a reference population [2,3]. Although segregation of SGA from normal is somewhat arbitrary, -2 SD was selected because it encompasses the majority of patients with disordered fetal growth. These babies can be sub-classified into SGA for weight, length, or for both weight and length [3]. SGA must be differentiated from low birth weight and intrauterine growth retardation (IUGR). A newborn short for his/her gestation may or may not be low birth weight. The term SGA refers not to fetal growth but to the size of the infant at birth whereas, the term IUGR suggests diminished growth velocity in the fetus occurring *in utero,* as documented by at least two intrauterine growth assessments. A child who is born SGA has not necessarily suffered from IUGR, and infants who are born after a period of IUGR are not necessarily SGA [4]. Separating small babies, who are small simply as a result of adaptation to maternal size, from those who have suffered IUGR, presents a diagnostic challenge. It is the IUGR group that is at an increased perinatal risk [5]. Pitfalls in recording accurate period of gestation, birth length and also non-availability of these records for later review are major challenges.

SGA children are at higher risk of attaining an adult height below their target height, as well as of developing metabolic disorders – obesity, diabetes and cardiovascular diseases [6,7]. These children are also prone to have precocious pubarche, exaggerated precocious adrenarche, an earlier onset of menarche, and faster progression of puberty than children born appropriate for gestational age (AGA) [8]. Developmental sequelae affecting the GH-IGF axis and adrenal and gonadal function are seen in children with abnormal weight gain during infancy and childhood [6,7]. Tempo of this postnatal weight gain is emerging as particularly important in the relationship between birth

weight and adult diseases [6]. There is lack of data not only on the SGA-associated co-morbidities, but also associated awareness about regular, long term follow up of these children in special clinics.

EPIDEMIOLOGY

The data on the incidence of SGA births are scarce in many countries because birth length and gestational age are rarely recorded in National databases. Based on the available data, it has been estimated that between 2.3 and 10% of all infants are born SGA [9]. India has a high incidence of low birth weight (LBW) and SGA babies [10-12]. The incidence of LBW in India is about 30% babies in contrast to 5-7% in developed countries [10]. A large percentage (approximately 70%) of LBW are SGA [10,13]. Kushwaha, *et al*. [11] studied 750 hospital deliveries (term singleton neonates) and found that 28.4% were SGA, which is almost similar to the incidence of 25% reported by Mehta, *et al*. [12]. Thus there is a huge burden of LBW and SGA in our country which needs to be addressed.

The causation of SGA is multifactorial. Fetal factors include chromosome abnormalities and genetic defects. Maternal factors involve age, weight and height, parity, chronic diseases, infections, impairment of nutritional status, and substance abuse. Placental factors include structural abnormalities and insufficient perfusion. Thus the ability to reach an optimal birth weight results from the interaction between the fetal growth potential (the fetal factors) and the environment (placental and maternal factors) [2]. The definition of SGA does not take into account the background growth-modifying factors such as maternal size, ethnicity, and parity. These factors may help in understanding the mechanisms and implications of being born SGA. Narang, *et al*. [14] in 1997 concluded that idiopathic intrauterine growth retardation is the commonest cause of SGA in Indian babies, followed by pregnancy induced hypertension which is one of the most important risk factors for SGA/IUGR.

GROWTH IN SGA

About 90% of SGA children show some degree of accelerated growth during infancy. In this context, rapid infant growth can be viewed as a compensatory mechanism for prenatal growth deficit, referred to as 'Catch-up growth'. Catch up growth is defined as weight or length gain greater than 0.67 SD score, which represents the width of each percentile band in standard growth charts, indicating clinically significant centile crossing [15,16]. Catch-up is typically an early postnatal process that in most SGA infants is completed by the age of two years. Different growth patterns may be identified in infants as young as three months [6]. While 80% of infants born SGA show catch-up growth during the first 6 months of life, 90% have catch-up growth with a height SD score of more than –2 by two years of age. Approximately 10% do not show catch-up growth, and most of these children continue to experience poor growth throughout childhood and remain short after the age of two years [4,17]. These individuals constitute a relatively high proportion of children and adults with short stature with a relative risk of 5-7 times than children born at normal size [17,18]. Karlberg, *et al*. [4] reported seven-fold increased risk of growth failure in SGA children, and it is said to contribute to 20% of the short adult population.

The mechanisms that allow catch-up growth in SGA children or prevent them from achieving normal height are still largely unknown. Nutritional or environmental insults in perinatal life can cause irreversible, long-term outcomes. The timing of such insults is significant in determining the extent of later adverse consequences to health. Three peptide hormones that share structural homology (IGF-I and -II and insulin) seem to be the most important endocrine regulators in early postnatal life. Low, *et al*. [19] suggested that catch-up growth in SGA children might be, at least in part, affected by intrauterine reprogramming of hypothalamic-pituitary-adrenal axis. Mother's height and weight are an important determinant of the adult height and weight of their children. SGA birth and their subsequent growth may also be the result of poor maternal nutrition, which is common in developing countries.

There is paucity of data on growth patterns in Indian SGA infants. There has been only one long term study on follow-up of low birth weight (LBW) infants reported from India, which was started in the late 60's on hospital-born urban cohort [10]. On evaluation of 79 premature AGA and 45 full-term SGA children, they found that the SGA remained significantly affected in their overall physical growth even at 14 years. In an unpublished study conducted at our institute over a period of two years from 2010-2012, of the 110 SGA babies enrolled between 12-18 months with mean age of 15 months, 62.7% (69) babies showed catch-up growth either in weight, length or both, and 37.3% (41) did not show any catch-up. On further stratification, 21.8% (24) showed catch up only in weight, 10.9% (12) only in length, and 30% (33) showed catch-up both in weight and length. Thus a total of 51.8% babies showed catch-up in weight and 40.9% in length [20,21].

PUBERTY IN SGA

Puberty is one of the most important milestones in life,

and involves growth spurt, changes in body shape and physiological functions. Being born SGA predisposes to a number of pubertal disorders like precocious adrenarche and puberties, and earlier onset of menarche. The timing as well as progression of puberty is linked to being born SGA. The main differences between the pubertal growth patterns of SGA and AGA children are that accelerated bone maturation and peak height velocity occur at an earlier pubertal stage in SGA children, resulting in a shorter duration of pubertal growth and a smaller than expected pubertal growth spurt. Though bone age maturation starts earlier in SGA children, it is not a reliable predictor of height potential in these children [8]. The important determinants of final height are the height and age at onset of puberty and the magnitude and duration of the pubertal growth [22], but the studies are scarce. Low birth weight is a risk factor for the later development of abdominal or truncal obesity, and SGA children with catch-up weight gain show a dramatic transition toward central adiposity, which enhances insulin resistance [23]. The sequence from low birth weight to precocious pubarche has been proposed to be a classic referral point in the progression to an early menarche followed by a polycystic ovary syndrome phenotype and, ultimately a shorter adult height [8]. One of the possible mechanisms responsible for this sequence may be early accumulation of visceral fat following postnatal catch-up growth, leading to insulin resistance and hyperinsulinism, which is thought to play a pivotal role in the development of a hyperandrogenic state in SGA girls [24]. Adiponectin, IGFBP-1 and triglycerides have also been implicated in the pathophysiology of obesity-related insulin resistance, glucose intolerance, and insulin-mediated lipoprotein metabolism. Hypoadiponectinemia has been associated with linear catch-up and is involved in pathogenesis of insulin resistance in SGA children; this may lead to precocious pubarche but only limited and conflicting information is available [23]. Jaquet, *et al*. [24] have also highlighted the critical contribution of adipose tissue in the metabolic complications in the SGA patient, with long-term consequences.

Children who show rapid postnatal weight gain have the highest adrenal androgen levels. In a retrospective Australian study of 89 children with precocious pubarche, 35% of the children were born SGA. The authors concluded that being born SGA according to weight and/or length is an independent risk factor for precocious pubarche [25]. Among the possible causes underlying this association are increased central adiposity, decreased insulin sensitivity and increased IGF-I levels between the ages of 2 and 4 years in SGA children with excess weight gain. According to the Avon Longitudinal Study of Parents and Children (ALSPAC), the combination of low birth weight and rapid postnatal weight gain had predicted increased total and central adiposity and higher IGF-I levels at 5 years of age, and lower insulin sensitivity at 8 years of age [26].

Most authors agree that puberty in short SGA children starts at a normal age, but relatively early for their short stature [27], yet the results are difficult to compare due to variations in SGA definitions, inclusion criteria, methodologies and follow-up periods. Several longitudinal follow-up studies comparing different groups of SGA and AGA children did not find any significant difference in the progression of puberty or age at menarche between girls born SGA and AGA [18,28]. However, other studies showed an earlier age of menarche in girls with fetal growth restriction relative to girls born with appropriate birth weight [29]. Ibanez, *et al*. [30] found that menarche before the age of 12 yrs was 3-fold more prevalent among girls born SGA (n=50); their age at menarche was advanced by 8-10 months compared with girls of normal birth weight. In an Indian study by Bhargava, *et al*. [10], menarche occurred 6 months earlier in the preterm group and 12 months earlier in the SGA group than in full-term AGA controls. Persson, *et al*. [31] reported that boys and girls born SGA were on an average 4 cm shorter at the onset of puberty than children without perinatal risk factors. Thus there is some evidence that pubertal height gain may be lesser than expected in children born SGA.

CONSEQUENCES OF BEING BORN SGA

Among SGA children who do not achieve catch-up growth by 2 year of age, the relative risk of short stature at 18 year of age is 5.2 for those born light and 7.1 for those born short [17].

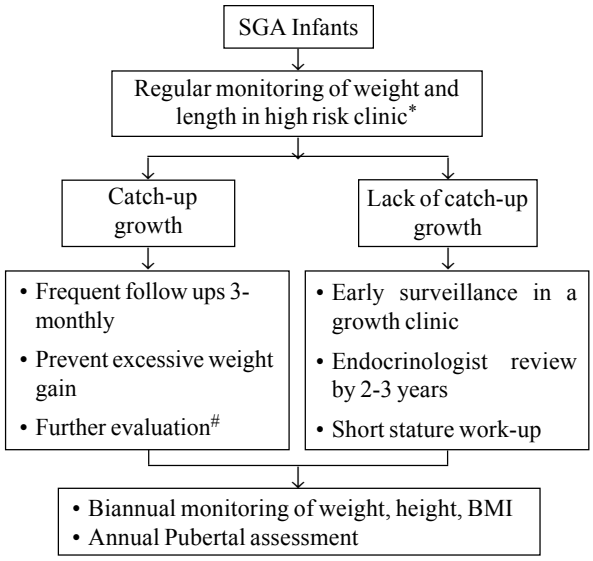
Low birth weight due to fetal growth retardation, and SGA children who experience rapid catch-up growth during childhood have been linked to development of the metabolic syndrome with all its diverse components (referred to as insulin resistance syndrome) – type 2 diabetes, hypertension, obesity, and hyperlipidemia. Barker, *et al*. [32] observed that the risk of metabolic syndrome at the age of 50 yr was 10-fold greater in individuals with a birth weight less than 2.5 kg than in those whose birth weight exceeded 4.5 kg. In another study, there were statistically significant differences in all components of the metabolic syndrome at 22 yr of age between the SGA and the AGA groups [33]. They found that 2.3% of individuals born SGA develop metabolic syndrome according to Adult Treatment Panel III criteria, compared with only 0.3% of individuals born

AGA. Furthermore, insulin resistance was significantly associated with other indicators of the metabolic syndrome, such as a high waist-to-hip ratio, hypertension, hypertriglyceridemia, and hyperglycemia [33]. Pubertal comorbidities in SGA are; higher risk for polycystic ovary syndrome, fertility problems, ovarian dysfunction, reduced fertility and early menopause [34,35].

FOLLOW-UP PLAN OF SGA BABIES

SGA babies should have a regular follow-up in high risk clinic for monitoring of their weight and length to prevent consequences of short stature, metabolic syndrome and altered puberty. The algorithm for follow-up and early surveillance has been briefly outlined in ***Fig*. 1**. Regular monitoring of weight, height, body mass index, and pubertal assessment during adolescence is particularly important. It is imperative to prevent excessive weight gain, which can be achieved through exclusive breast-feeding till 6 months, adequate maternal nutrition both intra- as well as post-partum and consumption of a low fat balanced diet as per individual's energy requirements. Breast feeding till two years of age not only slows the rate of weight gain in infancy, but also has a protective effect on long-term risk of obesity and intellectual impairment.

Growth hormone (GH) therapy has been used in SGA children with short stature with the aim of promoting growth, inducing catch up to normal height early, reducing the psychosocial problems and improving the social adaptation [17]. Intelligence and psychosocial functioning have been shown to be enhanced during GH treatment [36]. Huisman, *et al*. [37] concluded that there is a positive short-term effect of GH therapy on psychosocial functioning. It is proposed that SGA children aged between 2-4 year who show no evidence of catch-up with a height less than –2.5 SD should be eligible for GH treatment. Intervention with GH for those with severe growth retardation (height SD score, <–2.5; age, 2-4 year) should be considered at a dose of 35-70 µg/kg/day with higher doses for the ones with marked growth retardation. The use of GH in short children born SGA has been officially approved by the Food and Drug Administration in 2001 and by the European Agency for the Evaluation of Medicinal Products in 2003. Average height gain after 3 years of GH treatment range from 1.2-2.0 SD for doses of 35-70 µg/kg/d. There should be a positive response to GH treatment *i.e.* height velocity SD score more than +0.5 in the first year of treatment. In case of an inadequate response, re-evaluation is indicated. GH treatment is recommended till the growth rate falls to less than 2 cm/year [2,3]. Prasad, *et al*. [38] demonstrated a catch-up of +1.2 height SD score in SGA children with height for age Z-score <-2.5 who received GH for 2 years, and it was not associated with any significant adverse effects or acceleration of puberty. However, the use of GH in resource-restrained setting is still a matter of concern. Further, it remains to be determined whether GH therapy in short children who were born SGA has any beneficial or deleterious effect on their risk of developing metabolic syndrome in adulthood. GH therapy has been shown to have no effect on onset of puberty, progression of puberty, age at menarche and the interval between the onset of breast development and menarche. Although GnRH analog treatment might reduce growth velocity, evidence suggests that combined GH and GnRH analog treatment may improve adult height in SGA children who are short at the start of puberty (<140 cm) and have a poor adult height expectation, and they also need higher GH dose [39].



**Monthly follow up till 3 months of age, quarterly till one year of age, and then biannually until age of 8 years; #lipid profile, blood pressure, fasting and post-prandial glucose, fasting insulin levels, IGF-1, IGFBP 3, and adiponectin levels.*

FIG. 1 *Recommendations for follow up of SGA infants.*

Insulin sensitizer therapy has been proposed as potentially beneficial for SGA girls with early-onset puberty. Ibanez, *et al*. [40] published the effect of 36 months of Metformin therapy for SGA girls with early-onset breast development and it was found to be associated with slower pubertal development (prolonged time span between B2 and menarche), prolonged pubertal height gain and increased near-adult height. It was also associated with relatively lower insulin, leptin

and IGF-I levels and higher sex hormone-binding globulin and IGFBP-1 levels, as well as a less atherogenic lipid profile and leaner body composition.

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