



Small for gestational age and obesity related comorbidities

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Infant born small for gestational age (SGA) are at increased risk of perinatal morbidity, persistent short stature and metabolic alterations in later life. The result of SGA followed by rapid weight gain during early postnatal life has been associated with increased long-term risks for central obesity, insulin resistance, impaired glucose tolerance, type 2 diabetes, hypertension, increased fat mass, and cardiovascular disease. We should carefully monitor their weight during infancy and childhood to prevent excessive rates of weight gain. 'Healthy catch up growth' may decrease the risk of obesity-related comorbidities in SGA. Establishing the optimal growth patterns in SGA to minimize short- and long-term risks is important, and further studies will be needed. This review discusses recent studies concentrating on obesity-related morbidities in SGA infants that may provide insight into growth monitoring.

Keywords: Obesity, Small for gestational age, Metabolic syndrome

Introduction

Childhood obesity is an increasingly important public health issue both worldwide and in Korea. One potential predictor of later obesity is birth weight. Both small for gestational age (SGA) and large for gestational age (LGA) are correlated with obesity and obesity related morbidities over the course of an individual's life. Those who are born SGA are at risk of developing metabolic disease later in life, particularly obesity, insulin resistance, glucose intolerance, cardiovascular disease, and dyslipidemia.¹⁾ Approximately 85% of SGA infants achieve appropriate catch-up growth,²⁾ and they tend to gain weight more rapidly during the early postnatal period. Catch-up growth and accelerated postnatal weight gain is associated with an increased risk of adiposity and metabolic disease later in life.³⁻⁵⁾ This review discusses recent studies concentrating on obesity related morbidities in SGA infants that may provide insight into growth monitoring.

Obesity and SGA

An association between birth weight and development of obesity has been reported in numerous publications.⁶⁻¹²⁾ High birth weight is most strongly associated with subsequent childhood obesity.⁶⁾ SGA birth is also associated with greater adiposity (percentage body fat and fat mass), obesity, and particularly truncal obesity, in later childhood and adulthood.^{7,8)} Some studies have suggested that SGA infants remain lighter and have less body fat and others found them to be more likely to exhibit obesity in childhood, in particular with catch-up growth.⁹⁻¹²⁾ Older studies published from the 1970s to the 1990s, before the obesity epidemic that began in the 1980s, reported long-term reductions in height, weight, body mass index (BMI), and skinfold thickness in SGA.¹²⁾

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Effects of fetal growth retardation timing in SGA

Human development rates are highest during the first trimester of pregnancy. This period is essential for development of fetal cardiovascular and metabolic organs.¹³⁾ Smaller first trimester fetal crown to rump length was reported to be associated with higher total fat mass percentage, android/gynoid fat mass ratio, diastolic blood pressure, and total cholesterol concentration in childhood.¹⁴⁾ The observed associations suggest that the first trimester of pregnancy is a critical period for cardiovascular health in later life. One study documented that the exposure to famine in the first 2 trimesters of pregnancy is associated with increased obesity.¹⁵⁾ In contrast, those exposed to famine during the last trimester of pregnancy have reduced obesity rate.¹⁵⁾ The exact mechanisms for the associations of first trimester fetal growth and risk factors for cardiovascular disease remain unclear, but they may include changes in methylation of DNA and expression of RNA in response to a suboptimal fetal environment.¹⁶⁾

Adiposity in SGA

There are many reports showing an inverse association between birth weight and central fat deposition.^{7,17-20)} SGA infants have a continuously altered pattern of fat accumulation.²¹⁾ At birth, SGA infants included in the study had less adipose tissue than appropriate for gestational age (AGA) infants. Differences in anthropometric indices were continued until 6 weeks of age; however, adipose tissue distribution did not differ between AGA and SGA infants at that time.¹⁷⁾ When Harrington et al.¹⁸⁾ evaluated subcutaneous and intra-abdominal fat distribution in SGA, in contrast to the highly significant differences in subcutaneous fat tissue between AGA and SGA infants, they detected no significant differences in intra-abdominal adipose tissue. SGA infants exhibit a tendency to transition toward central adiposity, which enhances insulin resistance. Yoshikawa et al.¹⁹⁾ reported that the sum thickness of four skinfolds (triceps, biceps, suprailiac, and subscapular) in SGA infants was thinner at birth and caught up to AGA infants within 1 month, which supported a rapid postnatal catch-up fat phenomenon in SGA infants. Even though children born SGA remain slightly smaller than AGA children, they also exhibit reduced lean tissue mass without a reduction in fat mass, and thus have a higher percentage of body fat.⁷⁾ Also in adolescents, SGA could be associated with a higher subcutaneous truncal fat distribution.²⁰⁾

The mechanism of rapid postnatal fat accumulation in SGA infants has been investigated in some studies.^{19,22)} Some hormonal and metabolic factors may be related to early postnatal increases in fat accumulation. Lipoprotein lipase (LPL)-mediated lipolysis of very-low density lipoprotein (VLDL) and triglyceride (TG) may be one of the major mechanisms of rapid growth in subcutaneous fat tissue exhibited in SGA.¹⁹⁾ A rapid postnatal increase in LPL mediates

TG uptake from VLDLs.²²⁾ A marked postnatal increase in insulin-like growth factor-1 observed in SGA infants is one of the causes of rapid postnatal subcutaneous fat accumulation.¹⁹⁾

Role of catch-up growth/fat and obesity-related comorbidities in SGA infants

Catch-up growth refers to cross upwards by at least a one-percentile band on standard growth charts, equivalent to a gain in weight SD score of at least 0.67.⁴⁾ This catch-up growth may be advantageous for survival and may have long-term benefits with regard to cognitive development and stature.²³⁾ However, catch-up growth and rapid postnatal weight gain has been reported to be associated with an increased risk of adiposity and metabolic disease later in life.⁴⁾ Patterns in first-year weight gain seem to influence metabolic risk.^{24,25)} The effects of early, rapid weight gain are similar in non-SGA infants.^{26,27)} A study of young adults born AGA or SGA found that those who gained weight most rapidly (fast catch-up) during the first 3 months of life had the worst cardiovascular and metabolic risk profile.²⁸⁾ This sequence of SGA followed by fast catch-up in the first few months, which is the cell division period, has been reported to be associated with increased long-term risk for central obesity, insulin resistance, type 2 diabetes and cardiovascular disease.²⁹⁾

SGA and metabolic syndrome

The term metabolic syndrome refers to the presence of visceral obesity, dyslipidemia, impaired glucose tolerance or overt type 2 diabetes mellitus and hypertension as a cluster.³⁰⁾ The fetal origins hypothesis suggests that SGA infants are at higher risk of developing metabolic syndrome later in adulthood.³¹⁾ There are conflicting data regarding the association between SGA and metabolic syndrome in children, adolescents and young adults.³²⁻³⁴⁾ In a study of Korean adolescents, there were no differences in metabolic syndrome components among those that were SGA and non-SGA at birth, possibly due to different eating habits or racial traits.³⁴⁾

Low-birth-weight, but not catch-up growth, correlates with insulin resistance indices at 12 months, suggesting early occurrence of metabolic abnormalities.³⁵⁾ Early programming of insulin resistance plays a key role in the development of adult metabolic disease in those who are SGA at birth.³⁶⁻³⁸⁾ Insulin resistance or reduced insulin sensitivity may increase the risk of type 2 diabetes in adulthood, especially for SGA infants with catch-up growth and a high BMI.³⁹⁾ Higher levels of insulin are closely correlated with postnatal height catch-up growth in young SGA children and with weight catch-up growth in older children.⁴⁰⁾

SGA children with higher BMI were more insulin resistant than AGA children with similar weight and BMI.⁴¹⁾ Obese SGA children have higher fasting insulin, homeostatic model assessment-insulin resistance, glucose and insulin levels at 120 minutes after a glucose load compared with obese non-SGA

children.⁴²⁾ Overweight SGA children are also at increased risk of components of metabolic syndrome compared with overweight AGA children.⁴³⁾ These findings suggest that metabolic alterations in SGA are caused by both adverse fetal programming and obesity. In a recent study, school-age children and adolescents with combined fetal growth restriction and prematurity (preterm SGA) exhibited an increased prevalence of glucose risk and metabolic syndrome compared with term SGA or preterm AGA.⁴⁴⁾ This indicates that prematurity alone does not impact metabolic risk, while suggesting the influence of being born SGA.⁴⁴⁾

Evidence regarding lipid outcomes has been inconsistent.⁴⁵⁾ A meta-analysis showed a small but significantly inverse association between total cholesterol and birth weight.⁴⁶⁾ De Jong et al.⁴⁷⁾ reported a high prevalence of high triglyceride levels at 1 year of age in SGA children compared to AGA children. However, unlike insulin resistance, total cholesterol and low-density lipoprotein cholesterol levels were not significantly different between obese SGA and obese non-SGA children.⁴²⁾ Most studies reported no association between postnatal growth and lipid levels.⁴⁵⁾

Cardiovascular disease in obese SGA

The relationship between birth weight and coronary artery disease has been demonstrated in many studies.^{9,48-58)} Prenatal growth restriction can result in prenatal circulatory adaptations and altered heart and vascular tree development.⁴⁸⁾ Furthermore, hypertension in adult may be caused by a reduction in nephrons, decreased synthesis of elastin in the walls of the aorta, and large arteries due to fetal malnutrition.^{49,50)} Low birth weight has a tendency to cause high adult blood pressure.^{51,52)} However, cardiovascular disease risk in SGA children was not yet observed in blood pressure and laboratory measurements at age 6–12 years.⁹⁾

Leunissen et al.⁵³⁾ reported no associations between weight at birth and blood pressure at 21 years, but found positive association between weight gain and intima media thickness of the common carotid artery in young adults. This indicates that childhood weight gain, especially fat mass, rather than SGA itself has a greater influence on young adult blood pressure.⁵³⁾ There is a stronger association between low birth weight and the risk of coronary heart disease among men with high BMI at adolescence, compared with men with low BMI.⁵⁴⁾ This suggests that weight gain in adolescence may influence the relationship between birth weight and coronary heart disease.⁵⁴⁾ Intima media thickness of the common carotid artery, which is a well-known marker of subclinical atherosclerosis, was significantly increased in obese children born SGA compared with obese children born AGA of a similar age, sex and BMI.⁵⁵⁾

Healthy catch-up growth in SGA infants

As we reviewed above, rapid catch-up growth after birth in

SGA infants is related to a number of obesity related metabolic disorders. Persistent poor postnatal growth is associated with more frequent infection, short stature and impaired cognitive development in SGA.⁵⁶⁾ Lei et al.⁵⁷⁾ suggested that the optimal growth trajectory for SGA may be fast catch-up growth to about the 30th percentile in the first several months, with modest catch-up growth thereafter, to around the 50th percentile by 7 years old. Establishing the optimal growth patterns in SGA to minimize short- and long-term risks is important, and further studies will be needed. For healthy catch-up growth, nutrition guidelines and growth targets are also needed to balance associated risks.

Conclusions

The higher probability of SGA infants developing metabolic alterations could be related to both increased weight gain (catch-up growth) and fetal programming.⁵⁸⁾ Even with the same high BMI status, obese SGA individuals have more severe morbidities compared with obese non-SGA individuals. Gains in body fat mass, especially central fat might be predict adverse metabolic outcomes. Birth weight is an endpoint of different fetal exposures and growth patterns and the starting point of childhood growth. To prevent metabolic syndrome and cardiovascular disease, early interventions for obesity and routine monitoring of healthy growth is important in those born SGA. It may be necessary to evaluate metabolic parameters in overweight or obese SGA children.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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