Acta Biomed 2023; Vol. 94, N. 6: e2023220 DOI: 10.23750/abm.v94i6.15428

Endocrine and metabolic disorders in adolescent and adult patients born small for gestational age

Valentina Talarico, Angela Nicoletti, Giuseppe Raiola
SOC Pediatria, AOU "Renato Dulbecco", Presidio Pugliese, Catanzaro, Italy

Abstract. Children born small for gestational age (SGA), defined by a birth weight and/or length standard deviation score (SDS) of < –2 based on an appropriate reference population, represent a diverse group due to multiple underlying causes of reduced growth. This classification results in a heterogeneous patient cohort. SGA children are prone to endocrinological and metabolic issues not only in childhood but also extending into adolescence and adulthood. This population faces elevated health risks, including persistent short stature, premature adrenarche, pubertal development alterations, neurocognitive problems, and metabolic syndrome. Insulin resistance emerges as a pivotal factor contributing to these metabolic complications, prominently featuring obesity, insulin resistance, hypertension, and an increased risk of type 2 diabetes mellitus in adulthood. These medium- to long- term complications significantly impact their quality of life. Growth hormone (GH) therapy for short children born SGA facilitates height normalization throughout childhood, adolescence, and into adulthood. Catch-up growth, however, correlates with heightened risks of obesity, insulin resistance, and metabolic syndrome. Conversely, those without catch-up growth tend to exhibit pronounced short stature and cognitive dysfunction. Given these determinants, comprehensive management and clinical monitoring of SGA children should commence in the neonatal period and extend into adulthood. Recognizing and addressing these challenges early in life can mitigate the long-term impact on health and well-being, emphasizing the importance of a lifelong approach to their care.

Key words: SGA, short stature, metabolic syndrome, puberty

Background

Small for gestational age (SGA) is an auxological definition that characterizes neonates born with a birth weight and/or length below the normal range for gestational age.

There are several pathological conditions that can lead to an infant born SGA; they include various maternal, placental and genetic factors. Being the child of a young mother and/or father is the most common cause of SGA. Instead, the commonest pathological cause of SGA is considered to be placental dysfunction leading to suboptimal nutrition in utero (1).

The definition of SGA requires knowledge of gestational age, precise anthropometric measurements at birth, and appropriate reference data for birth weight and birth length. It is important to use national growth charts, when available, or those most appropriate for your specific region and ethnic population (2). It is also possible sub-classify the newborn SGA in three groups: SGA by weight, SGA by length, or SGA by both weight and length (3).

Infants born SGA with a small head circumference should be identified, as this may indicate specific etiologies. These sub-classifications can help understand the mechanisms and implications of the emergence of SGA (3).

These children may present several growth, hormonal, developmental peculiarities and metabolic problems possibly due to the growth restriction developed during pregnancy, which may lead to health consequences in later life, so a specific follow-up of these patients is required (4,5).

During adolescence and adulthood the main problems concern the persistence of short stature, the possible to having early onset and faster progression of puberty and early adrenarche and metabolic alterations (6,7). The metabolic and cardiovascular complications include cardiovascular disease and the insulin resistance syndrome, comprising dyslipidaemia, hypertension and impaired glucose tolerance or type 2 diabetes. These pathologies are strongly related to cardiovascular events in adults (8,9).

The objective of this review is to describe the main endocrine and metabolic problems of adolescents and adults born SGA.

Growth

Short stature is one of the most studied problems associated with SGA birth. The typical child born SGA experiences a period of accelerated linear growth during the first 12 months of life that results in stature being 2 SD greater by up to 90%. Most catch-up growth occurs during the first year and is almost complete by 2 years of age (4). Although most children born SGA show this catch-up growth, 10% will continue to have height below the 3rd centile throughout childhood, adolescence, and adulthood (10).

More recently, however, there has been increasing interest in the long-term adverse effects of this recovery phase of growth, or "catch-up growth." There is now compelling evidence that "accelerated" or too fast growth during critical or sensitive windows in early life has detrimental effects on long-term health, and particularly the risk of obesity and cardiovascular disease. In particular, accelerated growth, especially when it concerns weight gain (weight early growth acceleration), would not mean recovery but rather would be a negative phenomenon because it creates the conditions for precocious puberty and a tendency towards hypertension and insulin resistance in adolescence and adulthood (11,12)

Children born SGA are shorter during childhood and as adults, with a significant deficit in final height compared to children born appropriate for gestational age (4,13).

Previous longitudinal studies have shown a significantly reduced adult height with a five- to seven-fold higher risk of short stature among adults who were born SGA compared with adults born with appropriate size for gestational age (AGA) (13,14). Leger and colleagues, in a long term study, estimated that SGA males and females, respectively, were on average 3.99 and 3.64 cm shorter than their AGA counterparts(14). Furthermore, approximately 10-14% of people born SGA had short stature, that is, final height greater than 2 SD below the mean compared with only 1,8% of those born AGA (13,15).

In reaching the final height in born SGA children there are various factors and variables to consider. The strongest determinants of individual adult height in subjects born SGA were parental height and SDS birth length. Puberty does not appear to influence final adult height in subjects born SGA; in fact the difference between adult and prepubertal height SD scores was similar for the SGA and AGA groups (14).

Over the last decade, numerous clinical trials have shown that growth hormone (GH) therapy can increase childhood and, to a lesser extent, adult height for individuals born SGA. This has led to official indications by the Food and Drug Administration in 2001 and by the European Agency for the Evaluation of Medicinal Products in 2003 to approved the use of GH treatment for children born SGA, remaining short, with specific criteria (4,10,14).

Several studies demonstrate the positive effects of GH treatment on adult height in SGA children (1).

Van Pareren et al. (16) showed that, after 8 years of GH treatment, more than 80% of SGA children had an adult height within the normal and target height range. The mean overall height gain was between 1.8 and 2.1 SD, equivalent to a difference of between 9 and 14 cm between post-treatment adult height and pre-treatment predicted height using centilical curves. The growth in recovery was more evident in children who underwent more years of therapy and in those children who started therapy before the start of puberty.

The study by Dalhgren et al. (17) highlighted a gain of 1.7 DS (approximately 12 cm) in height in children treated more than 2 years before puberty versus 0.9 SD (about 9 cm) in those who started therapy later.

A systematic review published in 2009 identified 4 high-quality trials with adult height outcome in 391 short children born SGA treated with GH and showed a gain of 0.87 SD (5.7 cm) after 8 years of therapy compared to untreated children and a mean height gain in GH-treated SGA children versus untreated patients of 1.5 SD and 0.25 SD, respectively (10).

Puberty

There is some discord regarding the onset of puberty and its progression in adolescents born SGA. Studies have established that pubertal onset occurs earlier in children born SGA than in children born AGA (6,12), although timing appears appropriate for chronological age and height. Some studies have shown an onset of menarche 4 to 6 months earlier (1).

Pubertal alterations have been documented to occur in both sexes, but to be more pronounced in girls than boys, probably for more rapid effects of weight gain during childhood (18,19).

As regard the pubertal growth spurt, peak height velocity and duration of puberty were normal in SGA children, but the timing of peak height velocity occurred earlier in SGA boys and girls (1).

Bone maturation during puberty may be accelerated, peak height velocity may occur earlier and for a shorter period of time, fusion of growth plates may occur earlier. It has been hypothesized that this accelerated pubertal development is related to rapid weight gain in early childhood, which causes increased visceral adiposity, decreased insulin sensitivity, and elevated IGF-1 concentrations; therefore, children born SGA who have catch-up growth have a greater risk of early and accelerated puberty (6,18,19).

GH treatment in children born low SGA has been shown to have no effect on age at pubertal onset or progression of puberty.

Considering that children born SGA with rapid weight recovery and consequent increase in visceral adiposity more frequently present early puberty and rapidly progressive precocious puberty, weight control may represent a key element for the management of this problem. It is essential to act on adequate dietary control and increase physical activity in order to reduce the adverse metabolic effects of weight gain (6).

Other possible intervention options that have been suggested in literature are metformin or a Gonadotropin Releasing Hormone (Gn-RH) analogue combined with GH; however, these are not currently approved treatments.

Metformin promotes the control of central adiposity, insulin resistance and IGF-1 levels, which are pathologically associated with precocious puberty. A study highlighted how treatment with metformin for at least 3-4 years resulted in a delay in menarche of approximately 1 year, prolonged pubertal growth and an increase in adult height of 4 cm (20).

However, there is a lack of replication studies of off-label use of metformin to reduce adiposity and delay puberty in short children born SGA, and metformin is associated with gastrointestinal adverse events (6).

Regarding the off-label use of Gn-RH analogues to delay puberty during GH treatment, we have several studies available on patients born SGA, without evidence of adverse effects. In an important study, a group of infants born SGA with short stature at the onset of puberty, treated with Gn-RH and GH had final adult height similar to those who were taller at the onset of puberty or treated with only GH, suggesting that children born SGA who remained short at the onset of puberty may benefit from combined treatment with GH plus Gn-RH analogues (21).

In children treated with the Gn-RH analog, puberty began in the normal age range, although the duration of puberty after discontinuation of the Gn-RH analog was shorter than the duration in children treated with GH alone (6).

Thus, evidence for current therapies to modulate pubertal growth in children born SGA is limited and further studies are required (6).

Adrenal and gonadal function

Numerous studies have reported an association between SGA and premature or exaggerated pubarche. Premature adrenarche is characterized by elevated serum levels of DHEAS and/or androstenedione in the absence of premature pubarche, indicating possible alterations in adrenal function in SGA children without clinical evidence (1).

The onset of a similar picture of polycystic ovary syndrome in SGA adolescents is also possible, characterized by biochemical alterations even in the absence of evident clinical characteristics. Non obese girls born SGA had a ten-fold greater incidence of hyperandrogenism, follicle-stimulating hormone (FSH), luteinizing hormone (LH) alterations, anovulation, and hyperinsulinemia compared to lean AGA girls. Girls with low birth weight and early growth had signs of increased adiposity by 4 years of age and subsequently developed insulin resistance, increased visceral fat, dyslipidemia, increased dehydroepiandrosterone sulfate (DHEAS) and leptin levels, reduced globulin levels binding sex hormones and adiponectin (22).

Consistent with a risk for PCOS, serum SHBG concentrations were lower and testosterone concentrations higher in girls born SGA who regained weight, but LH, FSH, and estradiol concentrations were similar in adolescent girls born SGA and those born AGA (3).

Evidence of alterations in the hypothalamic pituitary gonadal axis exists in SGA children (1,22). These structural changes manifest as reduction in size of testes and ovaries, reduced uterine volume (1), however normal gonadal function was found in several SGA cohorts (3,23). Therefore, the available data do not support an impact of being born SGA on gonadal function and fertility (3).

Some studies conducted in small numbers of SGA subjects reported alterations in sex steroid synthesis and metabolism. Serum DHEA-S, androstenedione, FSH, LH, and serum testosterone concentrations were similar in both groups, but girls born SGA had increased estradiol and 17-hydroxyprogesterone concentrations. Short pubertal SGA boys and age-matched AGA boys had similar inhibin B and anti-Mullerian hormone (AMH) concentrations (3,23)

Thyroid and bone metabolism

A most important period for the skeletal development is the intrauterine third trimester as 80% of the bone mass formation in a newly born infant is acquired during this period.

Bone mineral density (BMD) is on average lower but within the normal range in person born SGA (3,24).

It was highlighted that individuals born SGA, both those with persistent short stature and those with spontaneous recovery, showed lower whole-body BMD (BMD-TB) compared to individuals born AGA; this data suggests that the reduction of BMD-TB is not only related to short stature but also depends on other determining factors that are disturbed in subjects born SGA (25).

This association declines significantly once adult height is reached with evidence of no correlation between low birth weight and significant risk of fractures in adults. In fact bone mineral apparent density of the lower spine (BMA- DLS) is similar in young adults born SGA or AGA (4).

Although thyroid disorders are described especially in preterm SGA at birth and in childhood and there is currently no clear evidence for major alteration of the thyroid axis in adolescent and adult born SGA versus AGA (3,4), in light of Spiegel et al. SGA thyroid problems can continue into childhood at least, and this should be remembered (26).

Metabolic problems

Epidemiological studies pointed out to the link between SGA children and the later risk of developing metabolic syndrome in the adulthood.

Metabolic syndrome or the insulin resistance syndrome is a cluster of metabolic abnormalities characterized by insulin resistance/hyperinsulinemia, abnormalities in glucose metabolism, dyslipidemia, hypertension, and obesity.

Four longitudinal studies that include a large cohort of young adults born SGA indicate a higher prevalence of metabolic syndrome, and higher risk of metabolically unhealthy body composition in those

who were born SGA and experienced a rapid weight gain in early life (3,27,28)

The exact mechanisms underlying the associations between fetal and early life growth and health later in life are mostly unknown.

One of the hypotheses is "the fetal origin hypothesis" by Barker et al.: they postulated that the events that occur during pregnancy leading to fetal malnutrition could result in permanent metabolic changes in the fetus. These metabolic changes are beneficial during fetal life, but might result in diseases in adulthood (29).

In several studies, Barker et al. (30) have noticed an association of low birth weight with alteration of glucose metabolism in adult life. Indeed a temporal relationship exists between birth weight and insulin sensitivity.

Impaired development in fetal life which is manifested as thinness at birth is associated with insulin resistance (reduction in insulin sensitivity) in adult life. Insulin resistance predisposes to several metabolic diseases including type 2 diabetes mellitus.

This led to the theory that proposed a higher risk for type 2 diabetes mellitus in later life for individuals born with a low birth weight.

Some author proposed the "thrifty phenotype hypothesis": they hypothesized that compromised fetal nutrition could make the growing individual nutritionally thrifty and subsequently lead to insulin resistance and deficiency. Glucose regulation was normal if under nutrition continued during postnatal life. But, postnatal exposure to over nutrition exposed defects in β-cell function and insulin sensitivity, ultimately leading to type 2 diabetes (1).

Among young adults born SGA, hyperinsulinemic euglycemic clamp demonstrated a reduction in insulin sensitivity, together with hypertriglyceridemia and increased truncal adiposity (7).

However there were no conclusive findings between rapid postnatal weight gain and lipids in middle childhood.

Risk for coronary heart disease in later life was related to the low birth weight in children, who stayed thin till 2 years of age with a rapid gain in BMI through childhood (31).

Adults born SGA, with a median age of 34 years, showed a markedly reduced exercise capacity compared to adults born AGA, but further research is warranted to find the cause and if there is an association with increased cardiovascular mortality (3,14).

Reduced prenatal growth was linked to later high blood pressure and this effect could be due to insulin resistance. A link had been proposed between low birth weight and vascular development. It had been postulated that there is a deficiency in the synthesis of elastin in the walls of aorta and large vessels of growth retarded fetuses and this could lead to change in the mechanical properties of the vessels and could result in loss of compliance. This could predispose these individuals to a higher blood pressure. Children and young adults born with a low birth weight demonstrated endothelial dysfunction (32).

The levels of inactive renin were lower in those born with a lower birth weight and in the babies who had a smaller abdominal circumference at birth; lower level of inactive renin was associated with higher systolic and diastolic blood pressures at 50–53 years.

One large population-based study, using data of the Swedish Medical Birth Registry from 1973 to 2003, showed an increased risk of severe preeclampsia in women born SGA (odds ratio 1.62 [95% CI, 1.32-2.02]) (3,28).

Epidemiological studies showed an association between birth weight and risk of cancer, in particular testicular cancer and hepatoblastoma (33). However, the evidence in favor of an association between SGA and cancer risk is weak and based on a single epidemiological study (3). These facts point to a need for pediatricians for carefully follow-up these children born SGA to preventing the development of excessive weight gain.

It is recognized that any risk for metabolic disorders associated with SGA can be amplified by the presence of other risk factors, such as weight gain, ethnicity, and family history. Therefore, routine evaluation of metabolic parameters is not justified in all children born SGA.

Metabolic parameters, such as fasting plasma glucose, oral glucose tolerance test, and lipid profile are only recommended in children with overweight (BMI ≥ 1 SDS) or obesity (BMI ≥ 2 SDS), those with a family history of type 2 diabetes mellitus, or when clinical signs suggest a metabolic disease.

Another important factor to analyze is the effect of GH therapy on metabolic parameters both during treatment and after its suspension.

Treatment with growth hormone could change body composition and insulin resistance that could have long-term effects for these children. In fact, GH therapy in SGA subjects determines a further decrease in insulin sensitivity with a compensatory increase in insulin secretion due to the antagonistic effects of insulin on GH (3).

However, long-term treatment with GH in large study groups showed that glycated hemoglobin (HbA1c) concentrations remained within the normal range and that none of the subjects born with SGA treated with GH developed type 2 diabetes mellitus (34).

During treatment with GH there was a decrease in fat mass and an increase in lean body mass due respectively to the lipolytic and anabolic effects of GH; SDS blood pressure decreases, resulting from a decrease in matrix metalloproteinases (3). Total cholesterol and low-density lipoprotein cholesterol (LDLc) decrease during GH treatment, indicating a beneficial effect of GH treatment on lipid metabolism (8,35).

Few studies exist on the long-term cardio metabolic health of young adults born SGA after cessation of GH treatment due to attainment of adult height compared to appropriate control groups (3,8).

Extensive data come from a Dutch study of 199 young adults born SGA previously treated with GH, followed for 5-12 years after cessation of childhood GH treatment. Cessation of GH treatment was followed by a significant and persistent increase in fat mass, whereas lean mass decreased only during the first 6 months after GH withdrawal and remained stable thereafter. However, fat mass 5 and 12 years after discontinuation of GH treatment was similar compared to controls. There were no changes in insulin sensitivity, or in systolic and diastolic blood pressure. The beneficial effect of GH treatment on serum lipid concentrations was maintained for 5 years after GH discontinuation. In contrast, the beneficial effects of GH treatment on bone mineral density were lost after GH withdrawal. At 5 years after GH discontinuation, subjects born SGA previously treated with GH had similar lipid concentrations, BMD, and prevalence of metabolic syndrome compared to untreated controls (8). Upon discontinuation of GH treatment, young adults born SGA should be counseled to adopt a healthy diet and lifestyle with regular exercise to avoid excessive weight gain and to maintain or preferably improve lean body mass. Long-term medical and metabolic follow-up of previously GH-treated young adults born SGA is only recommended in those with risk factors for metabolic and/or cardiovascular disease.

Quality of life

Health-related quality of life (HRQoL) reflects the perception of health as the physical, emotional and social well-being of an individual, and is a relevant outcome to assess the course of different pathologies and the efficacy of the treatments used (5).

Several studies have highlighted how SGA adults achieve lower professional and economic goals than those born with an adequate weight, but there is no difference in the degree of life satisfaction or marital status. Some works have obtained similar results in the HRQoL assessment, measured with the SF-36 questionnaire, in SGA persons compared to individuals born with adequate weight; others instead showed lower scores (5).

The study by Bertal et al highlighted how 32-year-olds born with VLBW reported a lower HRQoL than their peers born at term. This was observed in general health, physical functioning, role limitations due to physical and emotional problems, mental health, and physical component summary. It found that physical and mental health trajectories from 20 to 32 years of age showed an overall decline for VLBW adults while remaining stable in the control group (36).

In SGA patients without recovery of growth, some studies report a better quality of life after treatment with GH in correlation with their increase in height, showing a HRQoL similar to that of the control population or improving their previous scores (10,35).

The study by Rodrigez et al. (5) demonstrated that adult SGA patients who had not had a growth recovery have a compromised HRQoL, especially in the areas of mental health; however, this impairment is not related to the height achieved or other parameters

related to GH treatment. The specific involvement of mental health sectors suggests that these patients should be studied for neuro-cognitive and psychiatric problems that could influence HRQoL in adulthood.

This pathology can worsen during adolescence and adulthood. However, Rodriguez's study found the best mental health values of the SF-36 during an older age at the time of completing the questionnaire and in the years since the end of treatment, which could be interpreted as increasing resilience to problems faced with age (5).

Summary

This comprehensive review explores the multifaceted challenges faced by individuals born SGA across their lifespan, emphasizing endocrine and metabolic implications. Longitudinal studies reveal a heightened risk of short stature in adulthood, necessitating targeted interventions. GH therapy emerges as an effective approach, with studies demonstrating significant height gains. Pubertal dynamics in SGA adolescents, marked by early onset, present challenges. GH treatment shows no influence on pubertal timing, prompting a need for weight control interventions to manage associated complications.

Associations between SGA and premature pubarche or polycystic ovary syndrome-like conditions underscore endocrine complexities. While some alterations exist, overall gonadal function and fertility appear unaffected. Studies on skeletal development reveal lower bone mineral density in SGA individuals. However, this normalizes in adulthood. Thyroid function remains largely unaltered in SGA. Metabolic syndrome risks in adulthood, linked to SGA, are discussed. The fetal origin hypothesis and thrifty phenotype hypothesis provide frameworks for understanding metabolic changes.

Long-term effects of GH therapy on metabolic parameters are explored, revealing both benefits and considerations. Mental health nuances are explored and emphasize the need for neuro-cognitive assessments. Therefore, comprehensive assessments and interventions are crucial for optimizing the health and well-being of those born SGA across their lifespan.

Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethic Committee: Not applicable

Authors' Contribution: V.T., A.N. and R.G. contributed to the acquisition, processing and interpretation of scientific information and were involved in the drafting of the manuscript. V.T. and G.R. reviewed the entire process of defining and revising the manuscript. All authors have revised and approved the final version.

References

1. Cutfield W, Ayyavoo A. The Auxological and Metabolic Consequences for Children Born Small for Gestational Age. Indian J Pediatr. 2021;88(12):1235-40. doi: 10.1007 /s12098-021-03897-0.
2. Bertino E, Di Nicola P, Varalda A, et al. Neonatal growth charts. J MaternFetal Neonatal Med 2012 Apr:25 Suppl 1:67-9. doi: 10.3109/14767058.2012.664889.
3. Hokken-Koelega ACS, van der SteenM, BoguszewskiM, et al. International Consensus Guideline on Small for Gestational Age: Etiology and Management From Infancy to Early Adulthood.Endocr Rev. 2023;44(3):539-65. doi: 10.1210/endrev/bnad002.
4. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J ClinEndocrinolMetab. 2007;92(3):804–10. doi: 10.1210 /jc.2006-2017.
5. Rodrígez JMR, Toda LI, López ID, et al. Adult height and health-related quality of life in patients born small for gestational age treated with recombinant growth hormone. Sci Rep. 2023; 13(1):3135. doi: 10.1038/s41598-023-30281-z.
6. Netchine I, van der Steen M, López-Bermejo A, Koledova E, Maghnie M. New Horizons in Short Children Born Small for Gestational Age. Front Pediatr. 2021;13:9:655931. doi: 10.3389/ fped.2021.655931
7. Jaquet D, Czernichow P. Born small for gestational age: increased risk of type 2 diabetes, hypertension and hyperlipidaemia in adulthood. Horm Res. 2003;59(Suppl. 1):131–7. doi: 10.1159/000067848.
8. van der Steen M, Kerkhof GF, Smeets CCJ, Hokken-Koelega ACS. Cardiovascular risk factors and carotid intima media thickness in young adults born small for gestational age after cessation of growth hormone treatment: a 5-year longitudinal study. Lancet Diabetes Endocrinol. 2017;5(12):975–85. doi: 10.1016/S2213-8587(17)30311-X.

9. Goedegebuure WJ, van der Steen M, de With JL, Hokken-Koelega A. Cognition, health-related quality of life, and psychosocial functioning after GH/GnRHa treatment in young adults born SGA. J Clin Endocrinol Metab. 2018; 103(11):3931–8. doi: 10.1210/jc.2018-01463.
10. Maiorana A, Cianfarani S. Impact of growth hormone therapy on adult height of children born small for gestational age. Pediatrics. 2009;124(3):e519-31.doi: 10.1542 /peds.2009-0293
11. Singhala A. Long-Term Adverse Effects of Early Growth Acceleration or Catch-Up Growth. Ann Nutr Metab 2017;70:236–240. doi: 10.1159/000464302
12. Hvidt JJ, Brix N, Ernst A, et al. Size at birth, infant growth and age at pubertal development in boys and girls. Clin Epidemiol 2019;19(11):873-883. doi: 10.2147/CLEP.S217388.
13. Leger J, Levy-Marchal C, Bloch J, et al. Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study. BMJ. 1997;315(7104):341-7. doi: 10.1136/bmj.315.7104.341
14. Simon D, Léger J, Careljc. Optimal use of growth hormone therapy for maximizing adult height in children born small for gestational age. Best Pract Res Clin Endocrinol Metab. 2008;22(3):525-37. doi: 10.1016/j.beem.2008.03.003.
15. Adler E, Lambert AS, Bouvattier C, et al. Determinants of Final Height in Patients Born Small for Gestational Age Treated with Recombinant Growth Hormone. Horm Res Paediatr. 2021;94(1-2):52-62.doi: 10.1159/000516557.
16. Van Pareren Y, Mulder P, Houdijk M et al. Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial. J Clin Endocrinol Metab. 2003; 88(8): 3584–90.doi: 10.1210 /jc.2002-021172.
17. Dahlgren J, Wikland KA & Swedish Study Group for Growth Hormone Treatment. Final height in short children born small for gestational age treated with growth hormone. Pediatr Res. 2005; 57(2): 216–222. doi: 10.1203/01 .PDR.0000148716.71231.81
18. Saroufim R, Fuqua JS. The Variability of Growth and Puberty in Growth Hormone-treated Children Born Small for Gestational Age. J Clin Endocrinol Metab. 2022 Sep 28; 107(10):e4263-e4264. doi: 10.1210/clinem/dgac357.
19. Verkauskiene R, Petraitiene I, AlbertssonWikland K. Puberty in children born small for gestational age. Horm Res Paediatr. 2013;80(2):69-77. doi: 10.1159/000353759
20. Ibáñez L, Valls C, Ong K, Dunger DB, de Zegher F. Metformin therapy during puberty delays menarche, prolongs pubertal growth, and augments adult height: a randomized study in low-birth-weight girls with early-normal onset of puberty. J Clin Endocrinol Metab. 2006;91(6):2068–73.doi: 10.1210/jc.2005-2329.
21. Lem AJ, van der Kaay DC, de Ridder MA, et al. Adult height in short children born SGA treated with growth hormone and gonadotropin releasing hormone analog: results of a randomized, dose-response GH trial. J Clin Endocrinol Metab. 2012;97(11):4096–105. doi: 10.1210/jc.2012 1987.
22. Ibáñez L, López-Bermejo A, Díaz M, Marcos MV. Endocrinology and gynecology of girls and women with low birth weight. Fetal Diagn The. 2011;30:243–9. doi: 10.1159/000330366.
23. Boonstra VH, Weber RFA, De Jong FH, Hokken-Koelega ACS. Testis function in prepubertal boys and young men born small for gestational age. Horm Res. 2008;70(6):357-363. doi: 10.1159/000161866.
24. Lem AJ, van der Kaay DC, Hokken-Koelega AC. Bone mineral density and body composition in short children born SGA during growth hormone and gonadotropin releasing hormone analog treatment. J Clin Endocrinol Metab. 2013;98(1):77-86. doi: 10.1210/jc.2012-2492.
25. Smeets CCJ, van der Steen M, Renes JS, Hokken-Koelega AC. Bone Mineral Density After Cessation of GH Treatment in Young Adults Born SGA: A 5-Year Longitudinal Study. J Clin Endocrinol Metab. 2017;102(9):3508-16. doi: 10.1210/jc.2017-00269.
26. Spiegel E, Shoham-Vardi I, Sergienko R, et al. The association between birth weight at term and long-term endocrine morbidity of the offspring. J Matern Fetal Neonatal Med 2019;32(16):2657-2661. doi: 10.1080/14767058 .2018.1443440.
27. Leunissen RW, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA. 2009;301(21):2234-42. doi: 10.1001 /jama.2009.761.
28. Goedegebuure WJ, Van der Steen M, Smeets CCJ, Kerkhof GF, Hokken-Koelega ACS. SGA-born adults with postnatal catch-up have a persistently unfavourable metabolic health profile and increased adiposity at age 32 years. Eur J Endocrinol. 2022;187(1):15-26. doi: 10.1530/EJE-21-1130.
29. Barker DJP. The Fetal and Infant Origins of Adult Disease. Brit Med J.1990;301(6761):1111. doi: 10.1136 /bmj.301.6761.1111.
30. Barker DJP, Hales C, Fall CHD, Osmond C, Phipps K, Clark PMS. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia. 1993;36(1):62-7. doi: 10.1007/BF00399095.
31. Barker DJP, Osmond C, Winter PD, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2(8663):577-80. doi: 10.1016 /s0140-6736(89)90710-1.
32. Leeson C, Kattenhorn M, Morley R, Lucas A, Deanfield J. Impact of low birth weight and cardiovascular risk factors on endothelial function in early adult life. Circulation. 2001;103(9):1264–8. doi: 10.1161/01.cir.103.9.1264.
33. R. Spector LG, Puumala SE, Carozza SE, et al. Cancer risk among children with very low birth weights. Pediatrics. 2009;124(1):96-104. doi: 10.1542/peds.2008-3069.
34. Hokken-Koelega ACS. Risk factors for diabetes mellitus type 2 and metabolic syndrome are comparable for previously growth hormone-treated young adults born small for

gestational age (SGA) and untreated short SGA controls. J Clin Endocrinol Metab. 2007;92(1):160-5. doi: 10.1210/jc.2006-1073.
35. Bannink E, van Pareren YK, Theunissen NC, Raat h, Mulder PGM, Hokken-Koelega ACS. Quality of life in adolescents born small for gestational age: Does growth hormone make a difference? Horm Res. 2005;64(4):166–74. doi: 10.1159/000088792.
36. Berdal EK, Wollum AEK, Hollund IMH, et al. Health-related quality of life from 20 to 32 years of age in very low birth weight individuals: a longitudinal study. Health Qual Life Outcomes 2022;20(1):136. doi: 10.1186/s12955-022-02044-3.

Correspondence:
Received: 17 October 2023
Accepted: 18 November 2023
Valentina Talarico, MD
SOC Pediatria
Azienda Ospedaliero Universitaria “Renato Dulbecco”
Presidio Pugliese, Viale Pio X, 88100
Catanzaro, Italy
E-mail: talaricovalentina@gmail.com