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SPECIAL ARTICLE

Small for gestational age: concept, diagnosis and neonatal characterization, follow-up and recommendations

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Abstract Newborns who do not reach a weight appropriate for their gestational age and sex can be classified in different ways. This article defines the concepts of small for gestational age (SGA) and intrauterine growth restriction, as well as the underlying causes of these conditions, with the goal of establishing consensus definitions for these patients, in whom treatment with growth hormone throughout childhood may be indicated and who may be at risk of developing endocrine or metabolic disorders in puberty and adulthood. Most SGA children experience spontaneous catch-up growth that is usually completed by age 2 years. In SGA children who remain short, treatment with recombinant human growth hormone is effective, increasing adult height. Small for gestational age infants with rapid catch-up growth and marked weight gain are at increased risk of premature adrenarche, early puberty, polycystic ovary syndrome (girls), insulin resistance and obesity, all of which are risk factors for type 2 diabetes and metabolic syndrome in adulthood. The SGA status can affect different areas of neurodevelopment and manifest at different stages in life; neurodevelopmental outcomes are better in SGA infants

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with spontaneous catch-up growth. Due to the potential risks associated with SGA, adequate characterization of these patients at birth is imperative, as it allows initiation of appropriate follow-up and early detection of abnormalities.

PALABRAS CLAVE
Crecimiento recuperador;
Hormona de crecimiento;
Neurodesarrollo;
Pequeño para la edad gestacional;
Pubertad;
Resistencia a la insulina

Recién nacido pequeño para la edad gestacional: concepto, diagnóstico y caracterización neonatal, seguimiento y recomendaciones

Resumen Los recién nacidos que no alcanzan un peso acorde con su edad gestacional y sexo se pueden clasificar de distintos modos. En este artículo se definen los conceptos de pequeño para la edad gestacional (PEG) y crecimiento intrauterino reducido, así como las causas que las determinan con el objetivo de consensuar las definiciones en este tipo de pacientes que puedan ser susceptibles de tratamiento con hormona de crecimiento a lo largo de su infancia, así como de desarrollar patología endocrinológica en la pubertad y edad adulta. La mayoría de los niños PEG experimentan un crecimiento recuperador espontáneo que suele completarse a los dos años. En los PEG que no lo realizan, el tratamiento con hormona de crecimiento humana recombinante es efectivo, aumentando su talla adulta. Los PEG con crecimiento recuperador rápido y marcado en peso tienen mayor riesgo de desarrollar adrenarquia precoz, pubertad adelantada, síndrome del ovario poliquístico (niñas), resistencia a la insulina, y obesidad; predisponiendo al desarrollo de diabetes tipo 2 y síndrome metabólico en la edad adulta. La condición de PEG puede afectar diferentes áreas del neurodesarrollo y manifestarse éstas en diferentes etapas de la vida; los PEG con crecimiento recuperador espontáneo tienen mejor pronóstico neurológico. Los posibles riesgos descritos asociados a la condición de PEG hacen imperativo la adecuada caracterización de estos pacientes al nacimiento, que permitirá su seguimiento prospectivo y la detección precoz de alteraciones.

Introduction

Newborn infants who do not have a weight appropriate for their gestational age and sex can be classified in different ways, and the nomenclature used changes with these classifications. In the present document, we attempt to define all these terms and analyse the risk factors that increase the likelihood of this condition and how it should be managed, as these patients may benefit from treatment with growth hormone during childhood and be at risk of endocrine and metabolic disorders during puberty and adulthood.

Small-for-gestational-age concept. Differential diagnosis with intrauterine growth restriction

Based on the definition of the World Health Organization (WHO), the term *small-for-gestational-age* (SGA) applies to all newborn infants with a weight and/or length below the 10th percentile (P10) for gestational age and sex.[1] According to the consensus documents of different societies of paediatric endocrinology, including the one in Spain, newborn infants are considered SGA if their weight and/or length is 2 or more standard deviations below the mean (z score ≤ -2) for gestational age and sex in the reference population.[2,3] There have been attempts to establish the optimal threshold for SGA to predict an increased risk of mortality based on the weight percentile, with inconclusive results.[4] However, a recent study in infants born preterm before 32 weeks with birth weights below the 15th percentile (P15) found that outcomes were increasingly unfavourable as *z* score values decreased.[5]

The definition of SGA encompasses not only infants with intrauterine growth restriction due to obstetric issues that hinder foetal growth, but also genetically small children, that is, those who achieve their full growth potential. Also, two subgroups can be differentiated among SGA infants: those with both a low birth weight and low birth length, and those with either a low weight or a low length.

Intrauterine growth restriction (IUGR) refers to the condition of the foetus not achieving the intrinsic growth potential. It applies to foetuses with a decreased foetal growth velocity in 2 assessments that is below the P10 or at least 2 SDs below the mean in the reference population charts. In newborn infants, the definition of IUGR is based on an international consensus,[6] and applies to infants with a birth weight less than the third percentile on population-based growth charts or who meet at least 3 of the following criteria:

- Birth weight <P10 in population-based growth charts.
- Birth length <P10 in population-based growth charts.

Table 1 Classification of IUGR from an obstetric standpoint.

Stage I	Severe smallness or mild placental insufficiency	Some of the criteria: [-]EFW < P3 - CPR < P5 (2 assessments more than 12 h apart) - Umbilical artery PI > P95 - - MCA PI < P5 (2 assessments more than 12 h apart)
Stage II	Severe placental insufficiency	PFE < P10 and some of the following: [-]Absent end-diastolic flow in uterine arteries in >50% of cycles in a free-floating loop in both arteries in 2 assessments more than 12 h apart) - Reverse end-diastolic flow in aortic isthmus
Stage III	Low-suspicion foetal acidosis	EFW < P10 and some of the following: [-]Arterial: reverse end-diastolic flow in uterine arteries (in >50% of cycles, in both arteries and on 2 assessments >6—12 h apart) - Venous: PI in ductus venosus > P95, absent end-diastolic flow in ductus venosus or persistent venous dicrotic notching (in 2 separate assessments)
Stage IV	High-suspicion of foetal acidosis	EFW < P10 and some of the following: [-]Reverse end-diastolic flow in ductus venosus (in 2 assessments >6—12 h apart) - Pathological variation in CTG: - Short-term variation in FHR within 1 h in computerised CTG monitoring: - <2.6 ms between 26+0 and 28+6 weeks - <3 ms from 29+0 weeks - In absence of computerised CTG: <5 bpm over 1 h of monitoring - Deceleration pattern on CTG: ≥2 spontaneous every 10 min for 30 min

CPR, cerebroplacental ratio; CTG, cardiotocography; EFW, estimated foetal weight; FHR, foetal heart rate; MCA, middle cerebral artery; P, percentile (P3, P5, P10; P95); PI, pulsatility index.

- Head circumference <P10 in population-based growth charts.
- Prenatal diagnosis of fetal growth restriction.
- History of predisposing factors during gestation, such as maternal arterial hypertension, pre-eclampsia or congenital infection.

These are usually due to an unfavourable uterine environment, most frequently placental abnormalities that hinder foetal growth, although they can also be due to exposure to infection or toxic substances.

There are 2 types of IUGR:

- Symmetrical or proportionate: weight, length and head circumference all affected. It is usually due to intrinsic factor, such as genetic disorders or congenital infection.
- Asymmetrical or disproportionate: affects the weight or the weight and length with normal head circumference. It is usually due to abnormalities of placental blood flow usually starting from the second or third trimester.

Low birth weight (LBW) refers to newborn infants with a birth weight of less than 2500 g. The definition applies regardless of whether the birth weight is appropriate for gestational age and/or sex and consistent with the expected growth.

From an obstetric perspective, IUGR is classified into different stages, presented in Table 1.

Risk factors for small for gestational age

The main risk factors are genetic factors that contribute to decreased growth such as genetic disorders, malformations or congenital diseases, maternal factors and conditions that affect the function of the placenta (Table 2).

Approach to the assessment of the small for gestational age infant

Correct anthropometric measurement is crucial to assess outcomes in these infants:

Table 2 Risk factors that may contribute to SGA.

Maternal	Extreme age (<16 or >35 years)
	Low height and weight, malnutrition or undernutrition
	Parity (nullipara, grand multiparous, interval between pregnancies <6 months)
	Uterine malformations
	Previous history of SGA offspring
	Chronic HTN or pre-eclampsia
	Exposure to tobacco or other toxic substances (alcohol, opioids, cocaine)
	Use of pharmaceuticals (anticoagulants, antiepileptics, antineoplastics, antifolates)
	Infections (TORCH, varicella, malaria, syphilis, Chagas disease, listeria, HIV)
	Chronic diseases (renal failure, anaemia, lung disease, neoplasm, cyanotic heart disease, inflammatory disease)
Placental	Placental insufficiency, infarction or abruption
	Vascular anomalies
	Implantation defects
	Inflammatory abnormalities
Foetal	Chromosomal disorders (monosomy, trisomy, deletions, ring chromosome)
	Genetic disorders (achondroplasia, Bloom syndrome, Russel-Silver syndrome, etc.)
	Congenital malformations (cardiac, renal, etc.)
	Inborn errors of metabolism
	Congenital infection
	Multiple gestation

HIV, human immunodeficiency virus; HTN, hypertension; SGA, small for gestational age.

Weight

Place the neonate or infant on the scale, unclothed and without a diaper, trying to centre the weight evenly on the platform. Use of a digital scale accurate to 10 g is recommended. Two separate weight measurements should be made and the mean recorded or, otherwise, measurements should be repeated until 2 consistent measurements are obtained.

Longitudinal weight measurements should be made under consistent conditions: same time of day, in a stable and comfortable ambient temperature, without abrupt environmental variations and under the same physiological conditions in the patient (before or after a feeding, with an empty bladder). The weighing tray must rest on a level surface, with a nominal accuracy no greater than 0.1 g, and calibrated weekly.

In patients carrying medical devices such as vascular or urinary catheters, which are common in neonatal units, their use should be suspended during the measurement to prevent potential biases. If the weight of these devices is known, it should be subtracted from the total measured weight to obtain a more accurate estimate of the infant's actual weight.

The measurement used as baseline should be the birth weight or a measurement obtained within a few hours from birth to avoid bias due to physiological post-birth weight loss.

Length

Measuring the length in newborn infants requires the collaboration of two people and the use of a high-precision stadiometer. The measuring board has two vertical bases: a fixed head piece against which the infant's crown is positioned, and a sliding foot piece. Due to the inherent difficulty of measuring length, performance of multiple measurements (duplicated or triplicated) with calculation of the mean is recommended to maximise accuracy.

The infant must be placed in the supine position, with the body along the long axis of the board, ensuring that the shoulders and hips are in contact with the horizontal surface of the board and with the arms resting at the respective sides of the trunk. The head must rest on the board with the crown touching the fixed head piece, which stands perpendicular to the horizontal plane of the board, held in place by one of the measurers. At the same time, the other measurer uses one hand to carefully pull the legs of the infant straight, ensuring that the knees remain extended, while sliding the foot piece until it presses lightly but firmly against heel or heels of the infant, free of any obstruction, ensuring a 90 ° angle at the foot. Record the measurement to the nearest centimetre.

The baseline length value should be obtained 24–48 hours post birth to avoid potential bias due to caput succedaneum in infants born head first.

Using percentiles and z scores in neonatal assessments

Percentiles and *z* scores are essential tools in the assessment of growth and development in neonates and infants. Both provide a quantitative measure of how the measures in a given infant compare to those in a reference population, which allows early detection of potential anomalies or significant variations in growth.

Percentiles are statistical values that give the relative position of one observation within an ordered dataset. They

are widely used to assess weight, length and head circumference. For instance, a baby with a weight at the 50th percentile has a weight that is the same or greater than the weight of 50% of babies of the same age and sex in the reference population.

Standard deviation scores, also known as *z* scores, provide information about the dispersion of data in a distribution in relation to the mean. In neonates, *z* scores are used to quantify the variation of anthropometric measurements in relation to the mean value in the reference population. In a given distribution, a large standard deviation (SD) indicates greater dispersion of the values, while a small SD indicates that the values are more homogeneous. The *z* score corresponds to the number of SDs that a given value is above or below the mean within a normal distribution, thus providing a standardised measure that allows comparison of values across different distributions. A positive *z* score indicates that the value is above the mean, and a negative one that the value is below the mean. For instance, a *z* score of 1 shows that the given value is 1 SD above the distribution mean, while a *z* score of 1 indicates the given value is −1 SD below the mean.

Both measures, percentiles and *z* scores, are valid and widely used. The equivalence between these measures can be derived from the standard normal distribution, in which approximately 68% of the data are within 1 SD from the mean, 95% within 2 SDs and 99.7% within 3 SDs. Thus, it is possible obtain corresponding values for percentiles and *z* scores to interpret the anthropometric values measured in neonates in terms of their relative position within the distribution.

Recommended growth tables

There are numerous growth standards that can be used to assess growth for different anthropometric parameters. In extremely preterm infants, the SENeo recommends the use of the Fenton growth charts[7] during the neonatal period, as Spanish growth references do not include preterm infants born before 26 weeks of gestation. In term newborns, WHO growth standards are the most widely used reference[8]; however, the Sociedad Española de Endocrinología Pediátrica (Spanish Society of Paediatric Endocrinology), in agreement with the recommendations of the Ministry of Health of Spain, contemplates the use of the charts published by Carrascosa et al. because they were developed with data from the Spanish population.[9] This must always be taken into account, as subsequent growth in a child born SGA will be assessed using these charts.

Impact and short- and long-term risks

Postnatal growth

Most SGA children exhibit catch-up growth, most of it in the first 12 months of life and for the most part concluding by age 2 years, resulting in a height *z* score greater than −2 in approximately 90% of cases.[1] In SGA children born preterm, catch-up growth can take up to one year longer.[1,2] Small for gestational age children born very preterm or with a history of severe intrauterine growth restriction, especially those with small length at birth, are less likely to achieve an adult height in the normal range.[3]

The mechanisms underlying this change in growth have not been clearly elucidated. Growth hormone (GH) secretion is usually normal in patients born SGA, although basal levels may be high and the peaks may exhibit a high frequency and small amplitude. The levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding-protein 3 (IGFBP3) vary widely between patients, indicating a broad spectrum in the severity of GH insufficiency and resistance. However, none of the hormone levels serves as a predictor of potential catch-up growth, and the only variables that could be considered as having an impact on the adult height of these patients are the adult height and birth length of the parents.

Recombinant human growth hormone therapy

Treatment with recombinant human growth hormone (rhGH) in SGA children with inadequate catch-up growth is effective in increasing the final height.[1–3] In Europe, the use of rhGH has been authorised since 2003 for treatment of children born SGA without genetic syndromes and absent catch-up growth by age 4 years with a height *z* score of less than −2.5 and a height *z* score adjusted for the predicted adult height of less than −1. Growth hormone should be administered every day at night via the subcutaneous route. The effect is dose-dependent (increasing with increasing dose). The recommended dose is 0.035 mg/kg/day and can be increased to up to a maximum of 0.050 mg/kg/day.

There is ample evidence of the effectiveness of rhGH therapy in SGA children, with improvements in final height comparable to those observed in patients with GH deficiency.[1] Early initiation, a decrease in the height corrected for the predicted adult height and a larger dose of rhGH are the predictors associated with a favourable response.[1–7] Several studies, including some conducted in Spain, have shown that delayed initiation is associated with a significantly poorer response to treatment.[3,7–9]

The long-term safety of rhGH therapy has been the subject of debate. The Food and Drug Administration has reported that there is no conclusive evidence of long-term risks with the data currently available.[10,11]

Adrenarche and puberty

In children born SGA, there is a higher frequency of premature adrenarche (early start of the physiological increase in the secretion of adrenal androgens), which may or may not be associated with premature pubarche (pubic hair development before age 8 years in girls and 9 years in boys).

The incidence of precocious puberty (breast development at age 8–9 years in girls and increase in testicular volume >3 mL at age 10–11 years in boys) is also greater compared to the non-SGA population. These abnormalities are more frequent in girls and result from the mismatch between prenatal and postnatal weight gain.[12]

At birth, SGA infants have little subcutaneous fat (allowing the healthy storage of lipids obtained through dietary intake). If postnatal catch-up weight gain is rapid and excessive, the excess lipids are stored in ectopic fat deposits,

which may promote the development of insulin resistance, modify the proteomic profile of adipose tissue (adipokines) and increase serum IGF-I levels. In turn, this sequence of events promotes the synthesis of adrenal steroids and the occurrence of premature adrenarche and the synthesis of sex hormones and gonadotropins, leading to precocious puberty.[13–15] This can result in the premature closure of growth plates and a final height lower than the predicted height and, in some instances, lower than the target height.[13,15] The resulting abnormalities can further promote the development of polycystic ovarian syndrome (PCOS) in adolescence, which is a frequent cause of subfertility.[13]

The prevention and treatment of premature adrenarche, precocious puberty and PCOS involves the reduction of ectopic fat deposits through early weight control, a healthy diet and regular physical activity. Experimental studies have demonstrated that the reduction of ectopic fat and insulin resistance with metformin can normalise the endocrine-metabolic profile and the timing of puberty, delay the age of menarche, improve final height and prevent the development of PCOS.[14–16]

In adolescence, the internal genitalia of girls born SGA with and without catch-up growth may be smaller compared to female adolescents of the same age without a history of SGA. Higher concentrations of follicle-stimulating hormone, an increase in insulin resistance and decreased ovulation frequency have also been described in girls born SGA.[15] Some studies in male patients have suggested an increase in the future risk of testicular cancer,[16] but others have not found evidence of this association between decreased foetal growth and this type of cancer.[16]

Carbohydrate metabolism and cardiovascular system

The state of multiple hormone resistance that can result from IUGR can cause metabolic disorders, chief among them impaired insulin sensitivity, which is more pronounced the smaller the birth weight. Insulin secretion and sensitivity are intimately associated with the weight and height catchup patterns in the early months of life, and the risk of developing insulin resistance is greater the more rapid the postnatal catch-up growth, thereby increasing the risk of type 2 diabetes and metabolic syndrome in adulthood.[17–24]

Similarly, rapid catch-up growth is associated with changes in body composition and in adipose tissue that result in an increased risk of obesity, central adiposity and dyslipidaemia in adulthood.[24–30] There is also evidence of an increased risk of endothelial dysfunction[31] associated with an increased incidence of coronary disease and stroke in adulthood.[32]

All of these risks may be modulated by epigenetic factors.[33] An adequate diet that prevents excessive weight gain can prevent their development, which highlights the key role of exclusive breastfeeding in the first months of life, as it has a protective effect against the future development of these metabolic abnormalities; therefore, exclusive breastfeeding is recommended for all SGA infants from birth.[32–35]

Figure 1 Algorithm for the management of the SGA child.

Neurodevelopment, behaviour and learning

Intrauterine growth restriction gives rise to changes in endocrine function and a redistribution of blood flow that can compromise foetal brain development.[3]The potential complications resulting from it can affect different areas of neurodevelopment and manifest in different stages of the lifespan. In infancy and early childhood, the most frequent abnormalities involve motor function and coordination. From age 7 years, the impact may affect the intellectual quotient, memory and attention, with an increased incidence of concentration problems and learning difficulties.[3,36–38] A history of IUGR is also associated with an increased incidence of attention-deficit/hyperactivity disorder, behavioural problems and mood disorders, which may have a long-term impact on social functioning and employment.[38]

Small for gestational age infants with adequate spontaneous catch-up growth have better neurodevelopmental outcomes.[39] The role of early treatment with rhGH in infants without spontaneous catch-up growth has yet to be established.[40]

Conclusion

Due to the possible risks associated to SGA status described above, adequate diagnosis and characterization of infants with SGA during the neonatal period is an imperative, as it allows close monitoring during childhood and adolescence and the early detection of abnormalities.

Fig. 1 provides a graphic summary and key points for the follow-up of the SGA child, and Fig. 2 a graphic summary of the causes and consequences of SGA.

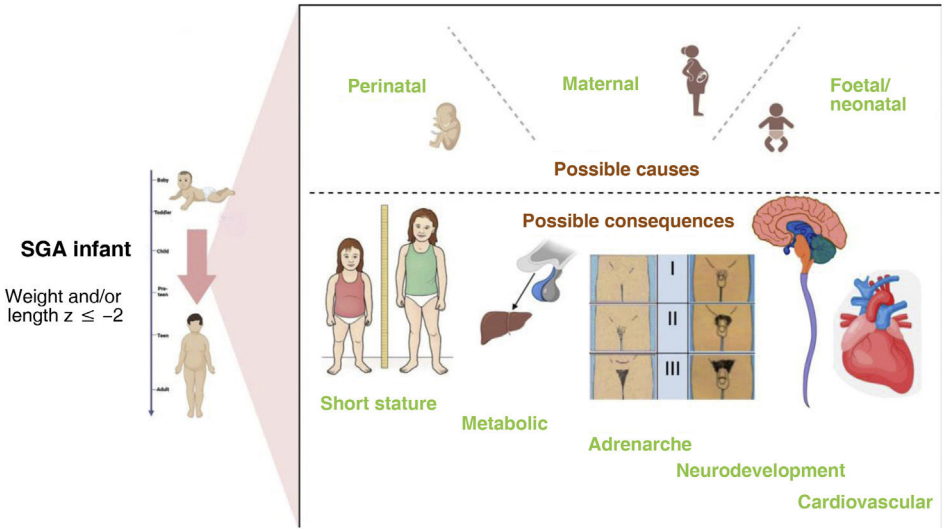

Figure 2 Causes and consequences of SGA.

Conflicts of interest

The authors have no conflicts of interest to declare.

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