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Review article

Children Born Small for Gestational Age

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SUMMARY

Introduction/Aim. Those born small for gestational age are all newborns whose weight, length and head circumference deviate by more than minus two standard deviations in relation to the same parameters of average children of the same sex, corresponding gestational age and population. The goal is their early recognition and adequate treatment. They should be clearly distinguished from premature babies, children born before the 37th week of gestation, and it should be noted that all children born small for gestational age are always born after intrauterine growth arrest. Poor and economically underdeveloped countries show a higher prevalence of children small for gestational age. At birth, these children have a higher risk of asphyxia, infections, neurological disorders, and in the later period of life, low growth, cognitive dysfunctions, disorders of pubertal development and metabolic syndrome. If they have not achieved growth compensation by the age of four and their height is less than minus 2.5 standard deviations, treatment with recombinant growth hormone is suggested. The recommended starting dose of growth hormone is 35 μg/kg of body weight per day. Adequate adjustment of the dose is achieved by monitoring the growth rate at 6 - 12 and IGF-1 at 3 - 6 months after starting therapy, and then once a year. The treatment is stopped in the period of adolescence, when the growth rate is < 2 cm per year.
Conclusion. Early recognition of children born small for gestational age provides the opportunity to avoid numerous complications later in life with adequate and timely treatment.

Keywords: **small for gestational age, newborn, growth, metabolic syndrome**

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INTRODUCTION

Children born small for gestational age (SGA) are those who, in relation to their corresponding gestational age, sex and population, have smaller body length (BL), body weight (BW) and head circumference (HC) (1). Due to postnatal specificities occurring in these children, it is necessary to recognize this condition early and have adequate supervision, monitoring and treatment during childhood, with the aim of minimizing possible complications during adulthood.

DEFINITION, INCIDENCE, AND ETIOLOGY OF SGA

The World Health Organization definition indicates that SGA children are those whose birth weight/length/head circumference is less than the 10th percentile for gestational age and sex in population, which corresponds to a value less than 1.28 standard deviations (-1.28 SD). If the gestational age is not estimated or known, it is also suggested that a newborn with a birth weight of less than 2500 g can be considered as an SGA newborn (2). Since this definition of SGA is not clear enough, pediatric endocrinologists suggest a definition of SGA in which birth weight/length/head circumference are less than 2 standard deviations (-2SD) for the child's gestational age, sex and population. With this definition, it is considered that a greater coverage of SGA children has been achieved with their more precise observation and monitoring in their further growth (3). There are also more detailed divisions among SGA infants, and they can refer to SGA for length, SGA for weight and SGA for head circumference (4). In order to adequately recognize SGA children, a unique definition of SGA, precise data on the gestational age of the newborn, accurate anthropometric measurements at birth, as well as reference percentile values for the population being evaluated are necessary (3).

Errors in the recognition of SGA children are often preterm infants, who are mischaracterized as SGA. Children born before the 37th week of gestation are defined as premature babies. Apart from the fact that premature babies are most often born SGA, they can also be born with appropriate (appropriate for gestational age-AGA), and very rarely with larger (large for gestational age-LGA) anthropometric birth measurements (BW/BL/HC) (1). That is why it is important to assess the exact gestational age as well as the birth measurements of the child after birth.

A term that is also often used in the context of SGA is IUGR (intrauterine growth restriction-IUGR). During intrauterine development, growth and development of the fetus may be delayed. Due to the action of various factors (maternal, genetic, nutritional or various external factors), the previous adequate development and growth of the fetus is stopped, that is, its further growth rate is reduced. The fetus does not grow properly, that is, it does not grow enough, which leads to restriction in intrauterine development, which can be accurately determined with two ultrasound measurements at least three weeks apart (5). Newborns with IUGR, as well as premature babies, are most often born SGA, but they can also be born AGA or LGA. SGA refers to children with smaller birth measurements, known gestational age and mostly without available information on the intrauterine growth of the child (1).

Early recognition, and initial identification of SGA children is of key importance for their further treatment. The gestational age of the newborn can be estimated based on the mother's anamnestic data on the first day of the last menstrual period, ultrasound examinations of the fetus during pregnancy, as well as during the first physical examination of the child in the maternity ward. Accuracy in the measurement of birth anthropometric measures (BW, BL, HC) is of great importance and should be performed according to standardized procedures. Birth anthropometric measures are compared with national reference percentile tables if available and updated with WHO data, upon which newborns are classified as SGA, AGA or LGA. Due to their specificities, special tables with anthropometric birth data are used for prematures babies and their classification is done accordingly(6 - 8).

In countries with low and middle gross national income in the last decade, 27% of live-born neonates were SGA, which represents about 30 million children. The prevalence of SGA ranges from 5.3% in East Asia to 40.5% in South Asia (9). Most SGA children are in Pakistan, India, Nigeria, Bangladesh. With the development and strengthening of the economy, the prevalence of SGA decreased over the years (10). In Europe, the prevalence in Finland is 3.1%, Italy 3.6%, in Sweden 5.7%, with a higher frequency among female newborns (11 - 13). The lack of consensus in defining SGA (< 10th percentile or < -2SD), the use of different national growth charts

within the population, and mixed ethics within one nation, often lead to confusion in the available literature about the actual prevalence of SGA children.

As risk factors for the occurrence of SGA, the age of the mother, parity, her height and weight, and ethnicity should be taken into account. SGA status is associated with pregnancy comorbidities such as gestational diabetes, oligohydroamnion, hypertension, and previous miscarriages (6). Factors such as alcohol use, smoking, drugs can also be important. The growth of the fetus will certainly depend on genetic factors as well as socioeconomic factors of the mother's environment (10). The explanation lies in the fact that richer and more economically stable women have a better standard of living, do less heavy physical work, are more educated, devote themselves more to proper nutrition and are more health-conscious (14).

COMPLICATIONS IN SGA CHILDREN

Infants born SGA are at five times higher risk of mortality in the neonatal period and 4.7 times higher risk of various diseases (asphyxia, lung dysfunction, infections or neurological deficits) during the first year of life (6). Problems faced by SGA children later in life include short growth, cognitive dysfunctions, premature adrenarche, disorders in pubertal development, disorders in lung and kidney function, development of metabolic syndrome in adulthood (3).

Although SGA children have a growth spurt in early childhood, later as adults they are usually 1 SD shorter than their target height. In the infant period, especially during the first 6 months, and somewhat less later until the second year of life, SGA children in more than 85% of cases reach a height that is above 2 SD (15). Recommendations for screening are regular anthropometric measurements (weight, height, head circumference) at 3 months in the first year and at 6 months in the second year. If the SGA children do not show accelerated growth in the first 6 months of life or their anthropometric measurements are ≤ -2SD even after two years, this status needs further assessment. It is necessary to rule out common pediatric diseases, genetic diseases as well as dysfunctions of the hypothalamus or pituitary gland. Premature babies who were born SGA sometimes need more than 4 years to reach their adequate height in relation to their age and gender (3).

The mechanism of postnatal growth in SGA children is complicated. Studies indicate disorders not only in the secretion of growth hormone (GH), but also disorders of the levels of basal values, peaks and amplitudes. The clear reason for these disorders is not known, although the role of GH in growth is increasingly significant only after the 6th month of postnatal life (16). Insulin-like growth factors (IGF) and its binding proteins are also important for the growth of SGA children. They were found to have lower concentrations in cord blood, as well as disorders at the level of the placenta (17). Assessment of bone maturation by ultrasound observation of the ossification grain in the femur has been observed as a prognostic possibility for height increase. If the ossification grain size is less than 3 mm, there is an intrauterine delay in bone maturation, and such SGA children will have faster postnatal growth, especially in the first 12 months of life (18).

Studies indicate that intelligence may be lower, but still within the normal range in SGA children. Their visual-motor perception is worse, and there are also disturbances when reading and calculating mathematical tasks (19). Through tests, SGA children show a lag in the development of gross motor skills, communication skills and cognition (20). It has been shown that reduced fetal growth is a significant indicator of later neurodevelopmental disorders of the child (21). Due to passive inattention and lower verbal intelligence, SGA children had poorer academic performance later in life (22). Behavioral problems, attention deficit hyperactivity disorder (ADHD) (23), aggression, anxiety and depression are just some of the disorders described in SGA (24).

Most SGA children have the onset of puberty in adequate time frames, but their growth is significantly slower during that period. The end result may be a lower target adult height. SGA boys may have more frequent hypospadias, cryptorchidism, and SGA girls may have adrenal androgen excess, hyperinsulinemia, or obesity (3). Due to rapid weight gain, SGA girls are at greater risk of adrenarche compared to AGA children. There were elevated concentrations of dihydroepiandrosterone sulfate (DHEAS), androgens, and insulin (25). Rapid postnatal growth and a large increase in body mass in early childhood (0 - 3 years) show higher levels of

androstenedione and DHEAS in the prepubertal period (26).

The presence of metabolic syndrome is characterized by the existence of disorders in the metabolism of lipids, glucose, elevated blood pressure, obesity of the central type, and the most significant is the existence of insulin resistance. SGA status has a common origin with metabolic syndrome, so it is also called "toddler syndrome". Lower concentrations of specific microRNAs in circulating SGA may play a role in epigenetic mechanisms of "metabolic disease programming in adulthood" (27). A rapid increase in postnatal body weight of SGA children in the first two years of life may later in adulthood cause a central type of obesity, with the existence of insulin sensitivity and altered beta cell function (28). The presence of signs indicating the development of metabolic syndrome and the existence of cardiovascular risk factors can occur in SGA children while they are still in the prepubertal period (29). In addition to the use of body mass index calculation for the purpose of detailed analysis of body composition and distribution of fat tissue, dual-energy x-ray absorptiometry (DEXA) is also used (3). A hypercaloric diet and childhood obesity can lead to serious health problems in SGA children later in life.

SGA TREATMENT

The treatment of SGA children is achieved using recombinant human growth hormone (rhGH) in the form of subcutaneous injections. The effects of various factors on the response to treatment have been shown. The dose of rhGH, the age of the child at the start of therapy, duration of treatment, as well as the height of the child at the beginning of treatment can play a significant role (30).

The use of rhGH was approved in 2001 in America by the Food and Drug Administration (FDA), in Europe in 2003 by the European Agency for the Evaluation of Medicinal Products (EMEA), while in Japan it was approved in 2008, and in Korea in 2014 (16).

Dosages of rhGH for the use in SGA children vary. According to the agreement of the International Society for Pediatric Endocrinology and the Society for Growth Hormone Research in Europe, the recommendations for initial doses are 35 μg/kg of body weight per day, while in America they range up to 68.5 μg/kg of body weight per day (3). The recommended rhGH dose range of 35 - 70 μg/kg BW per day allows clinicians to modify the rhGH dose, depending on the desired goal and treatment response. Exceeding the permitted ranges would bring minimal efficiency in growth promotion, but would contribute to a multiple increase in the risk of serious side effects of therapy (3, 31).

SGA children whose height is not too short can be treated in childhood with a dose of 33 μg/kg body weight per day until they reach adult height. In very short children (BH < -3SD), treatment would be more effective with higher doses of 50 μg/kg BW per day, as long as height growth is accompanied by weight gain in early childhood. Thereafter, dose reduction (up to 33 μg/kg BW per day) could be achieved by maintaining the absolute rhGH dose value in micrograms while there is an increase in the child's weight. The bottom line is that short-term growth in height would be provided by higher doses of rhGH, while long-term growth to adult height would be provided by lower doses (33 μg/kg BW per day) of rhGH (32).

In Europe, the use of rhGH is approved (EMEA) in SGA children older than 4 years if they are short (< -2.5SD) and have not had sufficiently accelerated catch-up growth. It is considered that this is a sufficient period (4 years) for a possible later start of catch-up growth in this population of children (3, 6). The minimum age approved for the use of rhGH is different in other countries: America (2 years of age), Japan (3 years of age), Korea (4 years of age), similarly as in Europe (16).

Reaching the optimal height of an SGA child can be achieved if there has been longer rhGH treatment before the onset of puberty. If the child is younger, shorter and weighs less, a better response to rhGH therapy is expected (33). Follow-up of SGAs treated with rhGH has shown a positive effect on blood pressure, lipid metabolism and nutritional status. Although without adverse effects on glucose and lipid levels, long-term rhGH therapy has been shown to induce insulin resistance. When the therapy is stopped, the insulin level returns to the reference values for age (34). RhGH treatment has its positive effect, not only because of its influence on reaching the target height, but also because of the possibility of influencing metabolic disorders. At the end of the treatment, it is possible for metabolic abnormalities to occur, but they appear only years later, usually in adulthood (35).

In order to effectively and adequately treat SGA children using recombinant growth hormone, it

is necessary to monitor their height. The parameter that indicates the right dose of rhGH is the child's growth response. The rate of height gain and height change is monitored every 6 - 12 months. It is also advised to control the level of IGF-1 in the serum for 3 to 6 months after starting the therapy, and then once a year. This provides more consistent information on patient adherence to prescribed therapy and rhGH dose compliance. Once a year, it is recommended to determine glycemic values, thyroid function, HbA1c and IGF-1. Monitoring of body mass index, blood pressure, level of lipid and glucose concentrations is advised in order to prevent the possibility of metabolic disorders (36).

An adequate response to therapy is necessary, which is manifested by a growth rate of +0.5 SD during the first year of treatment. Otherwise, the treatment is stopped while considering the adequacy of the rhGH dose. Recommendations for stopping further treatment are the period of adolescence, when the growth rate is less than 2 cm per year and the bone age is higher than 14 years for boys and 16 years for girls, due to the fusion of the epiphyses and cessation of further growth (3).

CONCLUSION

Anthropometric measurements and assessment of the gestational age of the newborn, as simple and accessible methods, provide the possibility of early recognition of SGA children, which can lead to their timely and adequate care. Treatment of SGA children using rhGH in adjusted individual doses allows avoiding numerous complications and provides them with a safer and better future.

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Deca rođena mala za gestaciono doba

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SAŽETAK

Uvod/Cilj. Rođena mala za gestaciono doba su sva novorođena deca čija težina, dužina i obim glave odstupaju za više od minus dve standardne devijacije u odnosu na iste te parametre kod prosečne dece istog pola, odgovarajuće gestacione starosti i populacije. Cilj je njihovo rano prepoznavanje i adekvatan tretman. Treba ih jasno razlikovati od prematurusa, dece rođene pre 37. nedelje gestacije, i imati na umu da se sva deca rođena mala za gestaciono doba uvek rađaju nakon intrauterinog zastoja u rastu. Siromašne i ekonomski nerazvijene zemlje pokazuju veću prevalenciju malih za gestaciono doba. Kod ove dece se po rođenju javlja veći rizik za asfiksiju, infekcije, neurološke smetnje, a u kasnijem periodu života veći rizik za nizak rast, kognitivne disfunkcije, poremećaje pubertetskog razvoja i metabolički sindrom. Ukoliko do svoje četvrte godine nisu nadoknadili rast i imaju visinu manju od minus 2,5 standardne devijacije, predlaže se lečenje rekombinantnim hormonom rasta. Preporučene početne doze hormonom rasta su 35 μg/kg telesne mase na dan. Adekvatno usklađivanje doze postiže se praćenjem brzine rasta na 6–12, a IGF-1 na 3–6 meseci po započinjanju terapije, a zatim jednom godišnje. Lečenje se prekida u periodu adolescencije, kada je brzina rasta < 2 cm godišnje.
Zaključak. Rano prepoznavanje dece rođene male za gestaciono doba pruža mogućnost da se uz adekvatno i pravovremeno lečenje izbegnu mnogobrojne komplikacije u kasnijem životnom dobu.

Ključne reči: **mali za gestaciono doba, novorođenče, rast, metabolički sindrom**