The Distinction between Constitutional SGA and FGR Infants

Subjects: Pediatrics

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Data regarding the nutritional management of preterm small for gestational age (SGA) infants are scarce. In the recent report of ESPGHAN, the recommended energy for very preterm infants during hospitalization has been increased, yet this may not fit the needs of all preterm infants. It is important to distinguish fetal growth-restricted (FGR) infants from constitutional SGA infants, as well as preterm SGA from preterm AGA infants, since they may have different nutritional needs. Preterm FGR infants, and specifically infants < 29 weeks' gestation, accumulate nutrient deficits due to intrauterine malnutrition, prematurity, morbidities, delayed initiation of feeding, and feeding intolerance. Therefore, these infants may need more aggressive nutrition for optimal catch-up growth and neurologic development.

nutrition preterm small for gestation age

1. Introduction

Although there is plenty of guidance for the nutritional management of preterm neonates, studies regarding the feeding of preterm small for gestational age (SGA) infants are scarce. Moreover, the special nutritional needs of preterm infants of multiple pregnancies, often SGA, are also practically missing. The ESPGHAN Committee on Nutrition of preterm infants has recently recommended to manage the nutrition of fetal growth restricted (FGR) or SGA infants in the same way as appropriate for gestational age (AGA) infants due to the paucity of data to propose specific recommendations. However, they also recommended an individualization of intakes [1].

However, preterm SGA infants may have different nutritional needs from preterm AGA infants, since preterm SGA infants often remain SGA at discharge, indicating accumulative nutrient deficits and failure to catch-up [2]. All preterm infants have deficits of important nutrients crossing the placenta mainly during the third trimester such as iron, calcium, vitamin A, and long-chain polyunsaturated fatty acids [3]. A preterm infant that is also FGR has experienced intrauterine malnutrition. Furthermore, comorbidities in the first days of life in preterm FGR infants, such as necrotizing enterocolitis (NEC) or feeding intolerance, often lead to delayed enteral feeding initiation [2][4]. Because of these factors, preterm FGR infants accumulate more nutrient deficits compared to preterm AGA infants. Furthermore, the combination of intrauterine malnutrition and excessive postnatal growth has been linked with metabolic changes and later adverse metabolic consequences in FGR infants [5][6]. All these factors render preterm FGR infants a special population with unique nutritional needs and a need for special nutritional management.

The two terms SGA and FGR should not be used as synonyms, since they refer to different conditions [7]. Various fetal, placental, maternal and genetic factors regulate intrauterine growth [8][9]. The definition of SGA includes infants with birth weight less than the 10th percentile, or at least two standard deviations below the mean for the infant's gestational age, based on data derived from a reference population [10][11]. This can be the consequence of a pathological process or can represent constitutionally small fetuses.

FGR defines a fetus that fails to reach his potential growth based on race and gender [9]. This term indicates that a neonate has undergone intrauterine malnutrition and growth compromise irrespective of their birth weight percentile [9]. This means that an AGA fetus can be also growth restricted if its intrinsic growth potential was higher [7]. These definitions are shown in **Figure 1**.

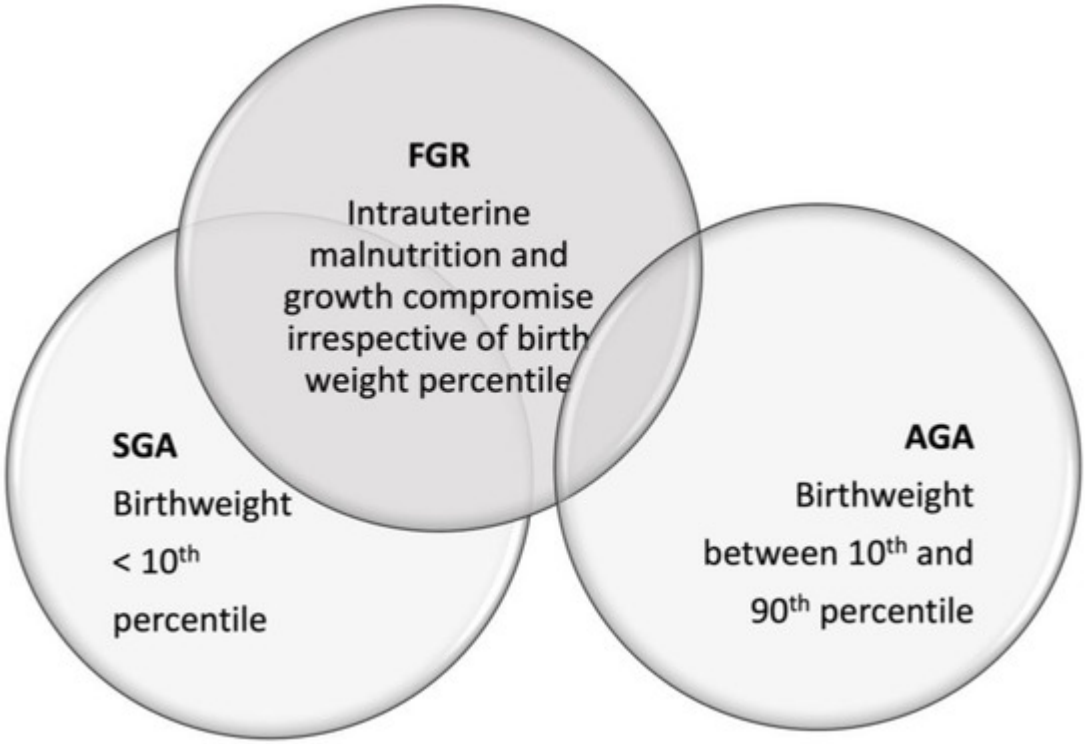

Figure 1. The definitions of small for gestational age (SGA), appropriate for gestational age (AGA) and fetal growth-restricted infants (FGR). Both SGA and AGA infants can be growth restricted.

It is challenging to assess the epidemiology of SGA and FGR infants, since some studies use the term SGA to refer to both FGR and constitutionally small infants. The incidence of SGA in well-resourced countries is 10% [12], while in low- and middle-income countries, almost 20% of term infants are SGA [13][14]. A recent study from cities in China found that the overall prevalence of SGA for 2014–2019 was 12.5% for term infants and 7.7% for preterm infants [15]. The prevalence of FGR is higher in resource-limited countries [14] and the incidence increases with decreasing gestational age [16][17]. Moreover, a significant part of all FGR occurs in AGA infants [7].

Even though FGR is a common condition, clear guidance for feeding these infants is lacking, and there is still debate on this subject. Studies addressing the optimal way of feeding FGR infants are scarce, and the terms SGA

and FGR are often used as synonyms, despite referring to different conditions. Moreover, multiple pregnancies are often complicated with intrauterine restriction, especially when growth charts for singletons are used.

2. The Distinction between Constitutional SGA and FGR Infants

It is important to distinguish FGR infants from constitutional SGA infants, since these two groups may have different nutritional needs. In the literature, SGA and FGR terms are often used as synonyms based on the idea that a small fetal size is associated with a higher possibility of growth restriction. However, the population is then diluted by healthy SGA fetuses and does not include AGA fetuses that are growth restricted [7]. On retrospective data, it is not possible to distinguish the two categories and exclude mature SGA infants. This is only possible in prospective studies that are designed to detect fetal growth deviations [18].

Ananth and Vitzileos hypothesized in their retrospective study that term SGA infants are mostly constitutionally small, while the group of preterm SGA may be comprised mainly by FGR fetuses, since biologic variability is not fully expressed at preterm gestations [19]. Large observational studies suggested that customized growth charts that adjust for the weight, height, ethnicity, and parity of the mother may be better compared to population-based charts in differentiating between constitutional SGA and FGR infants [20][21][22][23]. However, a Cochrane review in 2014 did not find randomized trials to assess the benefits and disadvantages of population-based growth charts compared with customized growth charts [24].

A 2016 consensus definition was established by experts in the field for the antenatal diagnosis of FGR through a Delphi procedure [25]. They concluded that an antenatal diagnosis of FGR includes an abnormal umbilical artery Doppler blood flow profile in addition to reduced growth velocity during fetal life. This means that both SGA and AGA fetuses can be diagnosed as FGR [25]. Furthermore, this consensus allowed for a distinction between early and late-onset FGR.

Therefore, constitutional SGA and FGR terms should not be used as synonyms, and studies in the literature have proposed effective ways to distinguish these two categories of infants.

The combination of poor fetal and accelerated postnatal growth rates in SGA infants appears to act in synergy in later metabolic adverse events [26]. In most SGA infants, catch-up growth occurs in the first 2 years of life and mostly in the first 6 months [27][28][29].

A systematic review of two randomized trials of term SGA infants concluded that enriched infant formulas that promoted early growth and contained 28–43% more protein and 6–12% more energy than the control formula increased fat mass, lean mass, and blood pressure at the age 5–8 years [30]. The authors of the two RCTs recommended that higher caloric intake and rapid weight gain are not optimal for these children, and therefore, breastfeeding should be preferred, since it was associated with slower weight and height gain [31][32]. However, a more recent systematic review of term SGA infants showed that children receiving exclusive breastfeeding had no

body composition alteration or increased insulin resistance compared to children receiving a higher calorie formula [33]. Therefore, it seems that breastfeeding should be preferred over enriched infant formulas in term SGA infants.

References

1. Supplementary Digital Content no.1. ESPGHAN Committee of Nutrition (CoN) Position Paper on Enteral Nutrition for Preterm Infants: Introduction, Methods and Limitations. Available online: http://links.lww.com/MPG/C974 (accessed on 6 April 2023).
2. Fleig, L.; Hagan, J.; Lee, M.L.; Abrams, S.A.; Hawthorne, K.M.; Hair, A.B. Growth outcomes of small for gestational age preterm infants before and after implementation of an exclusive human milk-based diet. J. Perinatol. 2021, 41, 1859–1864.
3. Shah, M.D.; Shah, S.R. Nutrient deficiencies in the premature infant. Pediatr. Clin. N. Am. 2009, 56, 1069–1083.
4. Dorling, J.; Kempley, S.; Leaf, A. Feeding growth restricted preterm infants with abnormal antenatal Doppler results. Arch. Dis. Child. Fetal Neonatal Ed. 2005, 90, F359–F363.
5. Chan, P.Y.; Morris, J.M.; Leslie, G.I.; Kelly, P.J.; Gallery, E.D. The long-term effects of prematurity and intrauterine growth restriction on cardiovascular, renal, and metabolic function. Int. J. Pediatr. 2010, 2010, 280402.
6. Martín-Calvo, N.; Goni, L.; Tur, J.A.; Martínez, J.A. Low birth weight and small for gestational age are associated with complications of childhood and adolescence obesity: Systematic review and meta-analysis. Obes. Rev. 2022, 23 (Suppl. S1), e13380.
7. Damhuis, S.E.; Ganzevoort, W.; Gordijn, S.J. Abnormal Fetal Growth: Small for Gestational Age, Fetal Growth Restriction, Large for Gestational Age: Definitions and Epidemiology. Obstet. Gynecol. Clin. N. Am. 2021, 48, 267–279.
8. Maulik, D. Fetal growth restriction: The etiology. Clin. Obstet. Gynecol. 2006, 49, 228–235.
9. Kesavan, K.; Devaskar, S.U. Intrauterine Growth Restriction: Postnatal Monitoring and Outcomes. Pediatr. Clin. N. Am. 2019, 66, 403–423.
10. WHO. Expert Committee on Physical Status: The Use Interpretation of Anthropometry & World Health Organization. In Physical Status: The Use of and Interpretation of Anthropometry, Report of a WHO Expert Committee; World Health Organization: Geneva, Switzerland, 1995.
11. Clayton, P.E.; 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. Clin. Endocrinol. Metab. 2007, 92, 804–810.

12. Lees, C.C.; Romero, R.; Stampalija, T.; Dall'Asta, A.; DeVore, G.A.; Prefumo, F.; Frusca, T.; Visser, G.H.A.; Hobbins, J.C.; Baschat, A.A.; et al. Clinical Opinion: The diagnosis and management of suspected fetal growth restriction: An evidence-based approach. Am. J. Obstet. Gynecol. 2022, 226, 366–378.
13. Lee, A.C.; Kozuki, N.; Cousens, S.; Stevens, G.A.; Blencowe, H.; Silveira, M.F.; Sania, A.; Rosen, H.E.; Schmiegelow, C.; Adair, L.S.; et al. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21(st) standard: Analysis of CHERG datasets. BMJ 2017, 358, j3677.
14. de Onis, M.; Blössner, M.; Villar, J. Levels and patterns of intrauterine growth retardation in developing countries. Eur. J. Clin. Nutr. 1998, 52 (Suppl. S1), S5–S15.
15. He, H.; Miao, H.; Liang, Z.; Zhang, Y.; Jiang, W.; Deng, Z.; Tang, J.; Liu, G.; Luo, X. Prevalence of small for gestational age infants in 21 cities in China, 2014–2019. Sci. Rep. 2021, 11, 7500.
16. Bernstein, I.M.; Horbar, J.D.; Badger, G.J.; Ohlsson, A.; Golan, A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am. J. Obstet. Gynecol. 2000, 182, 198–206.
17. Lemons, J.A.; Bauer, C.R.; Oh, W.; Korones, S.B.; Papile, L.A.; Stoll, B.J.; Verter, J.; Temprosa, M.; Wright, L.L.; Ehrenkranz, R.A.; et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001, 107, E1.
18. Fang, S. Management of preterm infants with intrauterine growth restriction. Early Hum. Dev. 2005, 81, 889–900.
19. Ananth, C.V.; Vintzileos, A.M. Distinguishing pathological from constitutional small for gestational age births in population-based studies. Early Hum. Dev. 2009, 85, 653–658.
20. Clausson, B.; Gardosi, J.; Francis, A.; Cnattingius, S. Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. BJOG 2001, 108, 830–834.
21. Mongelli, M.; Figueras, F.; Francis, A.; Gardosi, J. A customized birthweight centile calculator developed for an Australian population. Aust. N. Z. J. Obstet. Gynaecol. 2007, 47, 128–131.
22. Figueras, F.; Figueras, J.; Meler, E.; Eixarch, E.; Coll, O.; Gratacos, E.; Gardosi, J.; Carbonell, X. Customised birthweight standards accurately predict perinatal morbidity. Arch. Dis. Child. Fetal Neonatal Ed. 2007, 92, F277–F280.
23. Gardosi, J.; Chang, A.; Kalyan, B.; Sahota, D.; Symonds, E.M. Customised antenatal growth charts. Lancet 1992, 339, 283–287.
24. Carberry, A.E.; Gordon, A.; Bond, D.M.; Hyett, J.; Raynes-Greenow, C.H.; Jeffery, H.E. Customised versus population-based growth charts as a screening tool for detecting small for

gestational age infants in low-risk pregnant women. Cochrane Database Syst. Rev. 2014, 2014, Cd008549.

25. Gordijn, S.J.; Beune, I.M.; Thilaganathan, B.; Papageorghiou, A.; Baschat, A.A.; Baker, P.N.; Silver, R.M.; Wynia, K.; Ganzevoort, W. Consensus definition of fetal growth restriction: A Delphi procedure. Ultrasound Obstet. Gynecol. 2016, 48, 333–339.
26. Barker, D.J. The origins of the developmental origins theory. J. Intern. Med. 2007, 261, 412–417.
27. Karlberg, J.; Albertsson-Wikland, K. Growth in full-term small-for-gestational-age infants: From birth to final height. Pediatr. Res. 1995, 38, 733–739.
28. Recio Linares, A.; Bezanilla López, C.; Barasoain Millán, A.; Domínguez Uribe-Echevarría, M.; García Rodríguez, C.; Torrejón López, M.; Pérez Fernández, E.; Botija Arcos, G.; Barrio Merino, A. Longitudinal study of the newborn small for gestational age. Growth recovery and conditioning factors. Nutr. Hosp. 2022, 39, 520–529.
29. Campisi, S.C.; Carbone, S.E.; Zlotkin, S. Catch-Up Growth in Full-Term Small for Gestational Age Infants: A Systematic Review. Adv. Nutr. 2019, 10, 104–111.
30. Castanys-Muñoz, E.; Kennedy, K.; Castañeda-Gutiérrez, E.; Forsyth, S.; Godfrey, K.M.; Koletzko, B.; Ozanne, S.E.; Rueda, R.; Schoemaker, M.; van der Beek, E.M.; et al. Systematic review indicates postnatal growth in term infants born small-for-gestational-age being associated with later neurocognitive and metabolic outcomes. Acta Paediatr. 2017, 106, 1230–1238.
31. Singhal, A.; Cole, T.J.; Fewtrell, M.; Kennedy, K.; Stephenson, T.; Elias-Jones, A.; Lucas, A. Promotion of faster weight gain in infants born small for gestational age: Is there an adverse effect on later blood pressure? Circulation 2007, 115, 213–220.
32. Singhal, A.; Kennedy, K.; Lanigan, J.; Fewtrell, M.; Cole, T.J.; Stephenson, T.; Elias-Jones, A.; Weaver, L.T.; Ibhanesebhor, S.; MacDonald, P.D.; et al. Nutrition in infancy and long-term risk of obesity: Evidence from 2 randomized controlled trials. Am. J. Clin. Nutr. 2010, 92, 1133–1144.
33. Santiago, A.C.T.; Cunha, L.; Vieira, N.S.A.; Oliveira Moreira, L.M.; Oliveira, P.R.; Lyra, P.P.R.; Alves, C.A.D. Breastfeeding in children born small for gestational age and future nutritional and metabolic outcomes: A systematic review. J. Pediatr. 2019, 95, 264–274.