REVIEW ARTICLE

Extra-uterine Growth Restriction in Preterm Infants

Nitasha Bagga[1], Nalinikant Panigrahay[2], Akhil Maheshwari[3]

Abstract

Extra-uterine growth restriction (EUGR) is frequently seen in premature and critically ill infants. Even though advancements in neonatal intensive care have improved the survival of these high-risk infants, many new questions have emerged about the relationship between postnatal growth and neurodevelopmental outcome of these infants. EUGR has traditionally been ascribed to caloric restriction during postnatal periods of critical illness. Nutritional compromise, particularly during the first few weeks of life, may affect the overall growth and could also cause long-term neurodevelopmental impairment. The accidental and premature interruptions of pregnancy could also alter the normal mobilization and utilization of major nutrients from the ways that would have otherwise occurred during the last trimester of pregnancy, which is normally a period of maximal *in utero* growth. In this article, we review our current understanding of defining EUGR, various risk factors for EUGR, its pathophysiology, and possible ways with which our current healthcare protocols could prevent EUGR.

Keywords: Development, Growth restriction, IUGR, Premature, Skeletal.

Newborn (2022): 10.5005/jp-journals-11002-0019

Key Points

- Premature and critically ill infants often develop extra-uterine growth restriction (EUGR). In this article, we reviewed the risk factors, definitions, assessment of severity, and management of EUGR, and the likelihood of its association with altered neurodevelopmental outcome.
- We have briefly reviewed the association between changes in weight and skeletal parameters (skull growth, length).
- Chronic illnesses such as bronchopulmonary dysplasia, necrotizing enterocolitis, chronic liver disease, and cardiac conditions such as patent ductus arteriosus can alter postnatal growth.
- EUGR is usually secondary to chronic neonatal illnesses, but it may be a primary condition needing nutritional, medical, and genetic evaluation in some infants.

Introduction

Extra-uterine growth restriction (EUGR) is a "Nutritional Emergency" in preterm and critically ill term infants, which can arise from multiple clinical pathways and remains a challenge (Fig. 1). This term was first used in literature in 1982 by Hack et al. where weight <–2 *Z* scores at term gestation was used to define EUGR.[1] Subsequently, a few more groups were defined to have EUGR if their postnatal weight was <2 SD or <10th centile at 36 weeks or at discharge.[2,3]

Poor weight gain and EUGR have been associated with adverse medium- and long-term clinical outcomes. For instance, many studies have identified an association of poor in-hospital growth, whether it be in terms of weight gain,[4–6] length,[7,8] or head circumference,[4–6,9,10] with developmental delay. Even though causality remains unclear, these associations need study. The EUGR in some of the sicker infants could be rooted in feeding intolerance or in iatrogenic ultra-cautious provision of calories, but an alternative, equally valid explanation could also be in increased metabolic rates due to high severity of illness related to multiple comorbidities.[4,11–13] There are questions on whether education and course correction in nutrition could fully restore growth and prevent EUGR in the first scenario. We also do not know whether hyperalimentation in critically ill infants can, at least partially, mitigate the effects of increased metabolic rates and enable both weight gain and skeletal growth. Further study is needed before we can confidently tailor the nutritional strategies without adverse metabolic changes. We also need information to identify infants who are likely to respond to hyperalimentation.[14–16]

We need better definitions of EUGR. A recent review questioned the concept of defining EUGR based on only weight <10th centile at 36–40 weeks or at discharge.[17] In this article, we have extended this discussion and have included weight, skeletal, and cranial growth; modifiable and non-modifiable clinical associations; and the determinants of intrauterine growth. We also describe potential remedies to improve EUGR and the growth potential of these infants.

Defining EUGR

An accurate definition of EUGR is needed. As evident in literature, most of the studies defined EUGR based on weight at one point of time. It is important to appreciate that there is always biological variation in size of preterm infants; genetic determinants; social determinants; ante-, peri-, and postnatal morbidities; and inadequate nutritional support affecting the growth.[17] With the

[1,2]Rainbow Children's Hospital and Birthright, Hyderabad, Telangana, India

[3]Global Newborn Society, Clarksville, Maryland, United States of America

Corresponding Author: Nitasha Bagga, Rainbow Children's Hospital and Birthright, Hyderabad, Telangana, India, e-mail: nitashabagga@gmail.com

How to cite this article: Bagga N, Panigrahay N, Maheshwari A. Extra-uterine Growth Restriction in Preterm Infants. Newborn 2022;1(1): 67–73.

Source of support: Nil

Conflict of interest: None

evident literature, EUGR can be classified on the basis of consensus statement[18] and also described by Fenton et al. in their recent review[17] as "Identifying malnutrition in preterm and neonatal population-recommended indicators " of defining malnutrition in preterm infants. These classifications are shown in Table 1.

Extra-uterine Head Growth Restriction (EUHGR)

EUHGR is another important parameter to follow up in infants with faltering postnatal growth. It is defined as decreased head circumference-for age-Z scores to <2 SD, and has been associated with suboptimal neurodevelopmental outcomes.[4–6,10] The growth of the head circumference may be spared in some preterm infants with relatively recent onset of EUGR,[13,19] but other chronically undernourished infants may show restricted growth of all parameters, including head circumference, weight, and length. If there is a restriction in only the growth of head circumference but not in weight and length, there may be a need to evaluate for antenatal or postnatal neurological morbidities.[18] In preterm infants, post-discharge head growth may be more important as an indicator of cognitive outcome than in-hospital head growth.

Pathophysiology of EUGR

EUGR has been associated with multiple factors,[20] where one of the most critical ones is inadequate nutrition.[15] Despite consistent advancements to improvise preterm nutrition over decades, 28–97% of preterm infants develop EUGR as reported in various neonatal units.[21–23] Most of the nutritional determinants of postnatal growth are modifiable if followed rigorously.

- Modifiable risk factors of EUGR (Fig. 1):
  - Failing to meet required energy and protein needs during immediate postnatal period: Premature birth is the most critical period (third trimester) for nutritional accretion and rapid growth of fetus.[24] There is a considerable discrepancy in recommended daily intake (RDI) (to match the intrauterine growth) to the actual intake that builds up a cumulative mean energy and protein deficits within few weeks after birth.[15,25] Embelton et al. explained the cumulative energy and protein loss at the end of 5th week is around 813 ± 542 kcal/kg/day and 23 ± 12 g/kg respectively.[25] The nutritional goals during the initial days should seek to prevent the catabolism typically seen during the postnatal transition following preterm birth.
  - Variable nutritional practices: There is lack of consensus among individual neonatologists working in the same neonatal intensive care unit (NICU) and adhering to same nutrition protocol.[26] Variability in the time of initiation and amount of parenteral and enteral nutrition leads to poor accretion in these infants, cumulative energy and protein loss, and is the iatrogenic cause of EUGR.[27,28]
  - Overcautious increase of feeding volumes and frequent disruption of feeds: Neonatologists across the globe consider that delayed introduction, slow and cautious increase in feeding volumes may reduce the risk of necrotizing enterocolitis (NEC) in neonates.[29] This overcautiousness often leads to energy deficit and hence growth faltering. Likewise, the feedings are often interrupted in many infants with non-specific abdominal signs that are perceived as feeding intolerance. In many instances, the feeds are not re-initiated in a timely fashion.
  - Unintentional administration of low calories: In many premature infants born with lower-than-average birth weight, the nutritional goals may need to be carefully adjusted and if possible, aimed for the 50th percentile for that gestation.[30] Apart from this, many times the daily feedings may be below the RDI, as no changes in the amount of nutrients administered are made with respect to the increasing birth weight, which if continued for long periods causes cumulative energy and protein deficits.[24] Significant cumulative nutiritional deficit lies "in wait" in NICU as the clinicians hesitate about resumption of feedings.
  - Insufficient standard fortification: Breast milk is known to show considerable variation in nutritional content. Donor human milk, the next best option of milk for preterm infants if mother's own milk (MOM) is unavailable, is usually term milk or donated by mothers who are into many months of lactation. Thus, standard fortification may not be sufficient to meet the energy and protein needs of preterm babies because of the variability in mother's milk contents itself.[24,31,32]

Table 1: Classification of EUGR

Criteria	*Mild EUGR*	*Moderate EUGR*	*Severe EUGR*	*When to apply*
1. Weight-for-age *Z* scores[a]	Decline of 0.8–1.2 SD	Decline of >1.2–2 SD	Decline >2 SD	Not appropriate for first 2 weeks of life
2. Weight gain velocity[b]	<75% of expected weight gain for that particular age	<50% of expected weight gain for that particular age	<25% of expected weight gain for that particular age	Not appropriate for first 2 weeks of life
3. ≥2 of the following: • Length-for-age *Z* scores[a] • Length gain velocity[b] • Days to regain birth weight (in conjugation with nutrient intake)	Decline of 0.8–1.2 SD <75% of expected weight gain for that particular age 15–18 days (>3–5 consecutive days of <75% intakes of estimated protein/calorie)	Decline of >1.2–2 SD <50% of expected weight gain for that particular age 19–21 days (>5–7 consecutive days of < 75% intakes of estimated protein/calorie)	Decline >2 SD <25% of expected weight gain for that particular age >21 days (>7 consecutive days of <75% intakes of estimated protein/calorie)	Not appropriate for first 2 weeks, after that can be used in conjunction with other parameters if accurate length measurement is available Preferred for first 2 weeks of life

[a]Expected *Z* score for weight for age, length for age; [b]Weight gain velocity and linear growth velocity were estimated using online calculator (www.peditools.org). In this calculator, weight gain velocity is estimated by using the World Health Organization methods; Weight increments are classified by birth-weight category presented in 1- and 2-week intervals from birth to 60 days

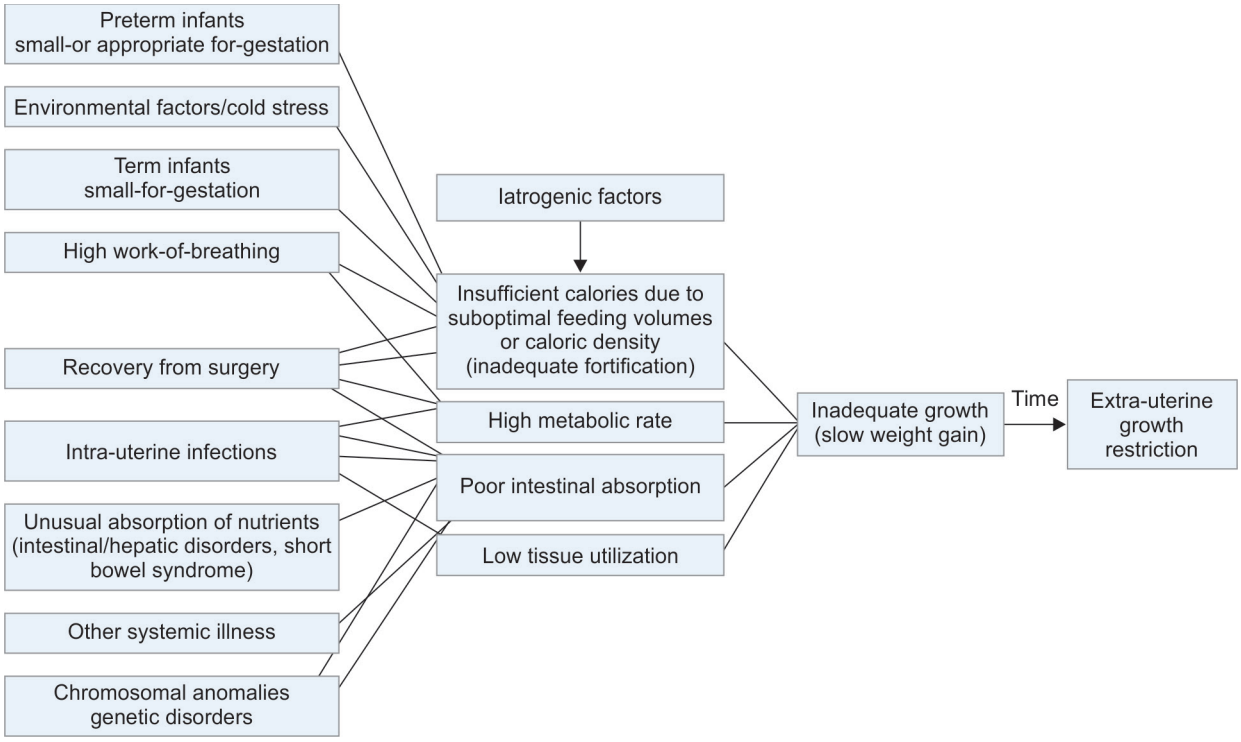

Fig. 1: Possible risk factors of EUGR (Extra-uterine Growth Restriction)

- Small for gestation (SGA): In preterm infants, particularly those who are also small-for-gestation, associated comorbidities may mandate frequent adjustments in feeding volumes. These babies, when cannot be given larger volumes of feeds, struggle with the similar concerns of inadequate protein and energy supply through routine fortification.[33]
- Multiple prematurity-related morbidities affecting growth during postnatal period: Prematurity is an important risk factor for EUGR, growth faltering, high morbidities, and poor neurodevelopmental outcomes.[14] Duration of hospital stay and ventilator support, bronchopulmonary dysplasia, patent ductus arteriosus, and NEC are independent risk factors for EUGR.[23]
- Postnatal growth failure in preterm and intrauterine growth retardation (IUGR) infants: Healthy fetuses who deliver at term do not encounter interruptions in nutritional supply, depletion of nutritional stores, deprivation of growth factors provided by mother and placenta, or increased energy consumption at the gestational ages that preterm infants have to experience *ex utero*.[34] Premature infants typically show considerable weight loss during the early neonatal period as feedings are still being established and due to multisystem illnesses mentioned above. However, even after achieving clinical stability, many do not achieve growth statistics similar to those of fetuses *in utero*, at least in terms of weight.[29,35] Similarly, many infants who were born Small for gestation (SGA) in terms of weight, length, and head circumference do not respond to nutritional interventions and continue to show EUGR. Some may even show worsening Z-scores from birth to discharge. More comprehensive measurements of total body composition are needed, at least in infants who are no longer on multiorgan system support. We are currently engaged in these measurements and should be able to report some data soon.

- Non-modifiable risk factors for EUGR
  - Epigenetic pathways and EUGR: EUGR is presumed to activate several reprogramming mechanisms. Various factors, both nutritional and environmental, regulate gene expression through epigenetic modifications[36–38] that might be responsible for intrauterine and extra-uterine growth. Tozzi et al.[39] reported that EUGR for weight and head circumference is associated with reduced intake of lipids and proteins in early days of life with hypermethylation of the IC1 (imprinting center 1) gene. Some authors emphasized that poor nutrition during the early part of life could be associated with epigenetic mechanism and underlined the relationship of decreased protein intake with DNA methylation.[40,41] In another study, Gong et al. highlighted the association of low maternal protein intake in animal models with IC1 methylation.[42] Once established, these epigenetic changes are difficult to reverse. Further research is needed to understand the value of these markers in EUGR for prognostication and as markers of response to potential therapeutic measures.
  - Plasma metabolome alterations and EUGR: Dudzik et al.[43] showed lower plasma levels of both essential and non-essential amino acids (especially branched chain amino acid) and several phospholipids (glycerophospholipids and sphingolipids) in EUGR preterm infants and also found further decline as per severity of EUGR (moderate >severe), which was irrespective of total parenteral and enteral nutrition in first week of life. Various bile acid metabolites were also found to be increased in severe EUGR infants, which could be hypothesized with the association of liver injury and growth failure. Further larger studies are required to understand the

pathways of growth failure in preterm infants and their long-term effects on developmental outcomes. These biomarkers may facilitate early identification of growth failure and help evaluate clinical/nutritional interventions.

- EUGR and genomic imprinting: Molecular alterations in parentally imprinted genes lead to various human imprinting disorders, which are associated with effects on intrauterine and postnatal growth. This knowledge of human imprinting disorders can be extrapolated to understand the complex regulation and interaction of genomic next-generation sequencing, transcriptomics, as well as methylomics in postnatal growth of preterm infants.[44]

Best Ways to Prevent EUGR (Fig. 2)

Prevention of EUGR in preterm neonates is one of the biggest challenges to neonatologists. Lack of standardized and evidence-based nutritional practices in a neonatal unit are the most common and modifiable risk factors responsible for EUGR.[15,20,21] The prerequisite in achieving optimal extra-uterine growth is the early identification of growth failure, timely intervention, and prevention. Although there are no evidence-based guidelines available, practice standardization and its consistent application can be done.[45,46] Various ways that can improve nutritional status of preterm infant and hence decrease the frequency of postnatal growth failure are as follows:

- Multidisciplinary nutrition support team: A team comprising neonatologists, nutritionists, lactation consultants, and dedicated nursing staff can strive to provide a consistent, individualized nutritional support to all neonates admitted in the nursery and provide a higher growth rate during NICU admission.[26,46] The support team can take the responsibility of regular nutrition specific rounds, growth chart plotting, and early identification of growth failure in preterm infants, which is an important milestone to prevent EUGR. Hence, it is advisable to have this support team observe and follow-up these babies during the hospital stay and after discharge for a sufficiently long period.
- Standardized feeding guidelines: Variation in the feeding practices guidelines in preterm infants is considered as one of the major determinants of postnatal growth failure.[47] It is recommended that every unit must have and strictly adhere to the standardized feeding guidelines to avoid discrepancies between the neonatologist and patient-to-patient variability. This approach helps in[48–50]
  - Immediate parenteral nutrition after preterm birth
  - Initiating feeding and guide to advance them
  - Rapid (or faster) achievement of full enteral nutrition
  - Manage feeding intolerance
  - Procedure and timing to introduce fortified human milk feedings
  - Reduction in the duration of parenteral nutrition

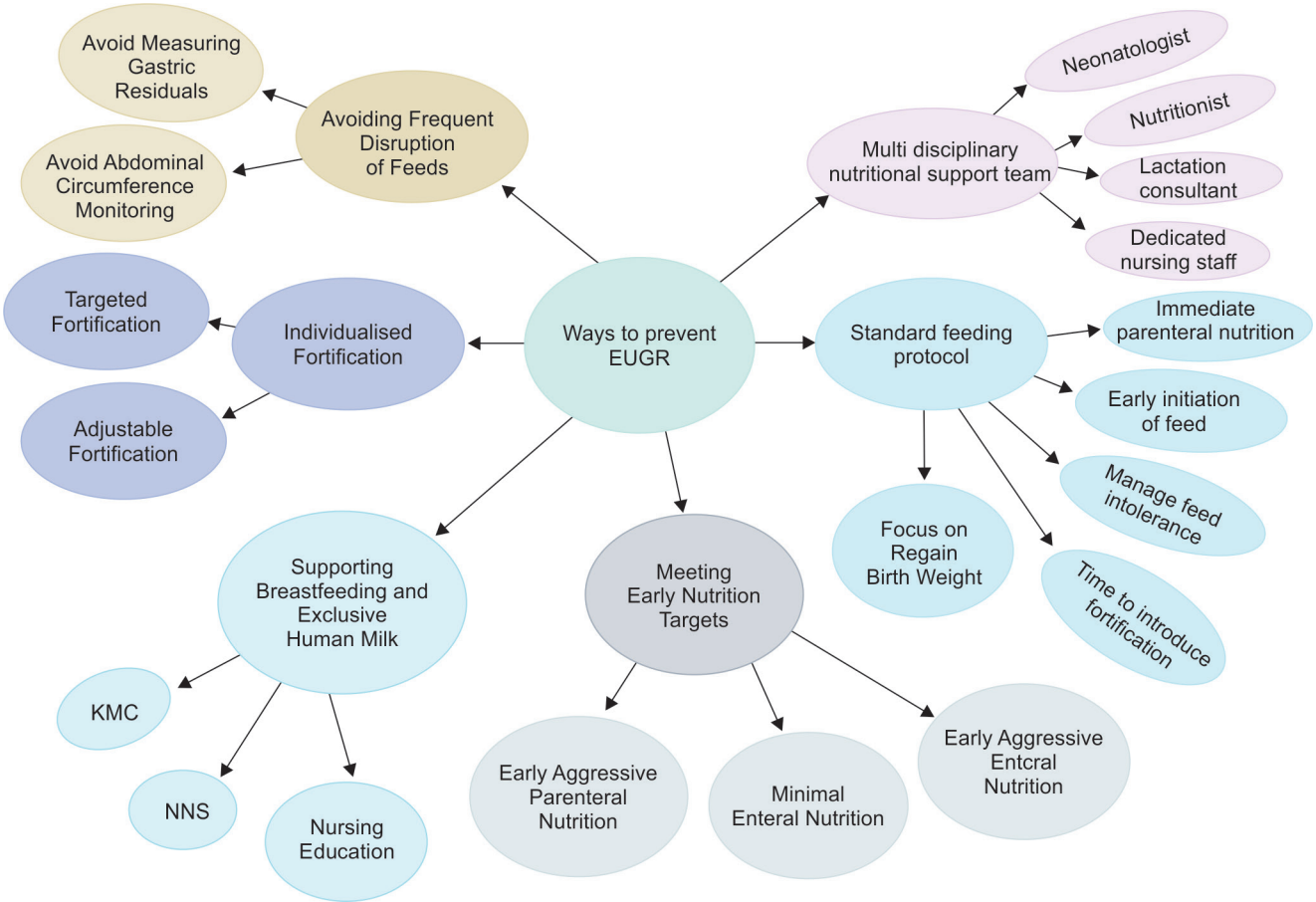

Fig. 2: Ways to prevent EUGR (Extra-uterine Growth Restriction) related to inadequate caloric intake

- Rapid regaining of birth weight
- Improved anthropometrics at 36 weeks' postmenstrual age (PMA).

Standardized feeding guidelines have been associated with lesser rates of NEC and late-onset sepsis, which are the two most important factors for growth failure in preterm infants.[51,52]

- Meeting early nutrition targets
  - Early aggressive parenteral nutrition: Immaturity of the gut in very preterm babies impedes enteral nutrition in adequate amounts during initial days. Early, aggressive parenteral nutrition not only minimizes the initial weight loss, cumulative protein, and calorie deficit during the acute, sensitive phase but also helps in improving the long-term growth and neurodevelopmental outcomes.[53,54] It is suggested to start amino acid in higher doses of 2–3 g/kg/day immediately after preterm birth.[55,56] along with lipids in dose of 1–2 g/kg/day in early hours of life[57] and subsequently increase the doses as recommended.
  - Minimal enteral nutrition: Minimal amounts of human milk (minimal enteral nutrition/trophic feeds) ranging from 10 to 20 mL/kg, starting as early as possible, must be a part of the standard feeding guideline. It is proven that early vs late (<48 hour vs >72 hour) initiation of enteral feeds significantly decreases the time required to reach full feeds, lesser time to regain birth weight, and shorter duration of total parenteral nutrition (TPN).[58]
  - Early aggressive enteral nutrition: In first 2 weeks of life, the EUGR group was given lesser enteral nutrition than non-EUGR group, which was correlated with healthy metabolomics profile (both amino acid and lipid profile) at the time of discharge in non-EUGR group.[43]
  - Supporting breastfeeding and ensuring exclusive human milk: Evidence-based, locally acceptable and relevant strategies to focus on exclusive MOM feeds should be made in every unit like antenatal and postnatal counseling, providing lactation support and educating mother for milk expression,[59,60] early and frequent pumping of milk,[61] role of Kangaroo mother care (KMC) and non-nutritive sucking (NNS),[62] and nursing education should be reemphasized.[63] Donor human milk (DHM) should be considered as the second best choice in the absence of MOM, as there is sufficient evidence in literature that DHM decreases the risk of NEC, chronic lung disease, retinopathy of prematurity and other prematurity-related morbidities, either used alone or along with MOM, when compared with formula feeds, which indirectly affects the postnatal growth outcomes.[64–66]
  - Targeted and adjustable fortification: Mother's milk alone is considered insufficient to meet the higher energy demands of preterm infants and hence, needs multicomponent fortification. It significantly helps in better weight gain, length, and head circumference,[67] safe in terms of feed intolerance and gastric emptying.[68] However, at the same time, standard multicomponent fortification may not be sufficient for adequate growth of these small premature babies.
  - Individualized fortification, which is a customized way of fortification guided by the growth and metabolic response of the baby, must be the focus of therapy.[69] This includes target fortification, adjustable fortification, and super-fortification.[70] However, none of these are considered ideal fortification, requiring further studies to formulize and draw optimal fortification strategies.
  - Avoiding frequent disruption of feeds: Altered gastric aspirates and increase in the abdominal girth are the most common causes for frequent disruption of feeds. It has been proven on various occasions that evaluations of gastric residuals delay the feeding process and can even damage the gastric mucosa.[71,72] Increase in abdominal circumference during prematurity is also variable and normal.[73] Therefore, frequent abdominal girth monitoring and checking gastric aspirates before every feed is not recommended.

Conclusions

Extra-uterine growth retardation should not be defined only on the basis of one-time weight assessment at 36–40 weeks or at discharge but all the three anthropometric parameters—weight, length, and head circumference—should be used together as an assessment tool for overall postnatal growth of preterm infants. Refinement in defining EUGR will not only help in appropriate growth assessments but also aid timely assessment of true growth faltering and interventions to deal with it. Lack of uniformity and inconsistency in nutritional practices are the most common causes. Nutritional assessment should be done on at least weekly basis during the NICU stay so that EUGR can be diagnosed and addressed timely. A lot of research is required to understand the deviation in body compositions of these preterm infants, which affects the postnatal growth than just to optimize and establish the recommended nutrition intakes.

References

1. Hack M, Merkatz IR, Gordon D, et al. The prognostic significance of postnatal growth in very low-birth weight infants. Am J Obstet Gynecol 1982;143(6):693–699. DOI: 10.1016/0002-9378(82)90117-x.
2. Shah PS, Wong KY, Merko S, et al. Postnatal growth failure in preterm infants: ascertainment and relation to long-term outcome. J Perinat Med 2006;34(6):484–489. DOI: 10.1515/JPM.2006.094.
3. Zozaya C, Diaz C, Saenz de Pipaon M. How should we define postnatal growth restriction in preterm infants? Neonatology 2018;114(2):177–180. DOI: 10.1159/000489388.
4. Franz AR, Pohlandt F, Bode H, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics 2009;123(1):e101–e109. DOI: 10.1542/peds.2008-1352.
5. Ehrenkranz RA, Dusick AM, Vohr BR, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117(4):1253–1261. DOI: 10.1542/peds.2005-1368.
6. Ong KK, Kennedy K, Castaneda-Gutierrez E, et al. Postnatal growth in preterm infants and later health outcomes: a systematic review. Acta Paediatr 2015;104(10):974–986. DOI: 10.1111/apa.13128.
7. Belfort MB, Gillman MW, Buka SL, et al. Preterm infant linear growth and adiposity gain: trade-offs for later weight status and intelligence quotient. J Pediatr 2013;163(6):1564–1569.e2. DOI: 10.1016/j.jpeds.2013.06.032.
8. Dusick AM, Poindexter BB, Ehrenkranz RA, et al. Growth failure in the preterm infant: can we catch up? Semin Perinatol 2003;27(4):302–310. DOI: 10.1016/s0146-0005(03)00044-2.
9. Sammallahti S, Pyhala R, Lahti M, et al. Infant growth after preterm birth and neurocognitive abilities in young adulthood. J Pediatr 2014;165(6):1109–1115.e3. DOI: 10.1016/j.jpeds.2014.08.028.

10. Raghuram K, Yang J, Church PT, et al. Head growth trajectory and neurodevelopmental outcomes in preterm neonates. Pediatrics 2017;140(1):e20170216. DOI: 10.1542/peds.2017-0216.
11. Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104 (2 Pt 1):280–289. DOI: 10.1542/peds.104.2.280.
12. Asbury MR, Unger S, Kiss A, et al. Optimizing the growth of very-low-birth-weight infants requires targeting both nutritional and nonnutritional modifiable factors specific to stage of hospitalization. Am J Clin Nutr 2019;110(6):1384–1394. DOI: 10.1093/ajcn/nqz227.
13. Sakurai M, Itabashi K, Sato Y, et al. Extrauterine growth restriction in preterm infants of gestational age < or =32 weeks. Pediatr Int 2008;50(1):70–75. DOI: 10.1111/j.1442-200X.2007.02530.x.
14. Ruth VA. Extrauterine growth restriction: a review of the literature. Neonatal Netw 2008;27(3):177–184. DOI: 10.1891/0730-0832.27.3.177.
15. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107(2):270–273. DOI: 10.1542/peds.107.2.270.
16. Wood NS, Costeloe K, Gibson AT, et al. The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. Arch Dis Child Fetal Neonatal Ed 2003;88(6):F492–F500. DOI: 10.1136/fn.88.6.f492.
17. Fenton TR, Cormack B, Goldberg D, et al. "Extrauterine growth restriction" and "postnatal growth failure" are misnomers for preterm infants. J Perinatol 2020;40(5):704–714. DOI: 10.1038/s41372-020-0658-5.
18. Goldberg DL, Becker PJ, Brigham K, et al. Identifying malnutrition in preterm and neonatal populations: recommended indicators. J Acad Nutr Diet 2018;118(9):1571–1582. DOI: 10.1016/j.jand.2017.10.006.
19. Tan MJ, Cooke RW. Improving head growth in very preterm infants–a randomised controlled trial I: neonatal outcomes. Arch Dis Child Fetal Neonatal Ed 2008;93(5):F337–F341. DOI: 10.1136/adc.2007.124230.
20. Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: a universal problem in preterm infants. Arch Dis Child Fetal Neonatal Ed 2004;89(5):F428–F430. DOI: 10.1136/adc.2001.004044.
21. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics 2003;111(5 Pt 1):986–990. DOI: 10.1542/peds.111.5.986.
22. Zhong QH, Liang K, He XY. [Nutrition status of premature infants in the neonatal intensive care unit and risk factors of extrauterine growth retardation]. Zhongguo Dang Dai Er Ke Za Zhi 2012;14(1):20–23. PMID: 22289746.
23. Shan HM, Cai W, Cao Y, et al. Extrauterine growth retardation in premature infants in Shanghai: a multicenter retrospective review. Eur J Pediatr 2009;168(9):1055–1059. DOI: 10.1007/s00431-008-0885-9.
24. Lima PA, Carvalho M, Costa AC, et al. Variables associated with extra uterine growth restriction in very low birth weight infants. J Pediatr (Rio J) 2014;90(1):22–27. DOI: 10.1016/j.jped.2013.05.007.
25. Embleton ND. Optimal protein and energy intakes in preterm infants. Early Hum Dev 2007;83(12):831–837. DOI: 10.1016/j.earlhumdev.2007.10.001.
26. Ziegler EE. Meeting the nutritional needs of the low-birth-weight infant. Ann Nutr Metab 2011;58 Suppl 1:8–18. DOI: 10.1159/000323381.
27. Grover A, Khashu M, Mukherjee A, et al. Iatrogenic malnutrition in neonatal intensive care units: urgent need to modify practice. JPEN J Parenter Enteral Nutr 2008;32(2):140–144. DOI: 10.1177/0148607108314373.
28. Hans DM, Pylipow M, Long JD, et al. Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey. Pediatrics 2009;123(1):51–57. DOI: 10.1542/peds.2007-3644.
29. McNelis K, Fu TT, Poindexter B. Nutrition for the extremely preterm infant. Clin Perinatol 2017;44(2):395–406. DOI: 10.1016/j.clp.2017.01.012.
30. Cooke R. Postnatal growth in preterm infants: have we got it right? J Perinatol 2005;25 Suppl 2:S12–S14. DOI: 10.1038/sj.jp.7211310.
31. Henriksen C, Westerberg AC, Ronnestad A, et al. Growth and nutrient intake among very-low-birth-weight infants fed fortified human milk during hospitalisation. Br J Nutr 2009;102(8):1179–1186. DOI: 10.1017/S0007114509371755.
32. Rochow N, Fusch G, Choi A, et al. Target fortification of breast milk with fat, protein, and carbohydrates for preterm infants. J Pediatr 2013;163(4):1001–1007. DOI: 10.1016/j.jpeds.2013.04.052.
33. Corvaglia L, Aceti A, Paoletti V, et al. Standard fortification of preterm human milk fails to meet recommended protein intake: bedside evaluation by near-infrared-reflectance-analysis. Early Hum Dev 2010;86(4):237–240. DOI: 10.1016/j.earlhumdev.2010.04.001.
34. Sauer PJ. Can extrauterine growth approximate intrauterine growth? Should it? Am J Clin Nutr 2007;85(2):608S–613S. DOI: 10.1093/ajcn/85.2.608S.
35. Corpeleijn WE, Vermeulen MJ, van den Akker CH, et al. Feeding very-low-birth-weight infants: our aspirations versus the reality in practice. Ann Nutr Metab 2011;58 Suppl 1:20–29. DOI: 10.1159/000323384.
36. Ruchat SM, Hivert MF, Bouchard L. Epigenetic programming of obesity and diabetes by in utero exposure to gestational diabetes mellitus. Nutr Rev 2013;71 Suppl 1:S88–S94. DOI: 10.1111/nure.12057.
37. Choi SW, Friso S. Epigenetics: a new bridge between nutrition and health. Adv Nutr 2010;1(1):8–16. DOI: 10.3945/an.110.1004.
38. Gonzalez-Rodriguez P, Cantu J, O'Neil D, et al. Alterations in expression of imprinted genes from the H19/IGF2 loci in a multigenerational model of intrauterine growth restriction (IUGR). Am J Obstet Gynecol 2016;214(5):625 e1–e11. DOI: 10.1016/j.ajog.2016.01.194.
39. Tozzi MG, Moscuzza F, Michelucci A, et al. Extra Uterine Growth Restriction (EUGR) in preterm infants: growth patterns, nutrition, and epigenetic markers. A pilot study. Front Pediatr 2018;6:408. DOI: 10.3389/fped.2018.00408.
40. Lillycrop KA, Phillips ES, Torrens C, et al. Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPAR alpha promoter of the offspring. Br J Nutr 2008;100(2):278–282. DOI: 10.1017/S0007114507894438.
41. Rees WD, Hay SM, Brown DS, et al. Maternal protein deficiency causes hypermethylation of DNA in the livers of rat fetuses. J Nutr 2000;130(7):1821–1826. DOI: 10.1093/jn/130.7.1821.
42. Gong L, Pan YX, Chen H. Gestational low protein diet in the rat mediates Igf2 gene expression in male offspring via altered hepatic DNA methylation. Epigenetics 2010;5(7):619–626. DOI: 10.4161/epi.5.7.12882.
43. Dudzik D, Iglesias Platas I, Izquierdo Renau M, et al. Plasma metabolome alterations associated with extrauterine growth restriction. Nutrients 2020;12(4):1188. DOI: 10.3390/nu12041188.
44. Eggermann T, Davies JH, Tauber M, et al. Growth restriction and genomic imprinting-overlapping phenotypes support the concept of an imprinting network. Genes (Basel) 2021;12(4):585. DOI: 10.3390/genes12040585.
45. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126(3):443–456. DOI: 10.1542/peds.2009-2959.
46. Maas C, Poets CF, Franz AR. Avoiding postnatal undernutrition of VLBW infants during neonatal intensive care: evidence and personal view in the absence of evidence. Arch Dis Child Fetal Neonatal Ed 2015;100(1):F76–F81. DOI: 10.1136/archdischild-2014-306195.
47. Stevens TP, Shields E, Campbell D, et al. Variation in enteral feeding practices and growth outcomes among very premature infants: a report from the New York State Perinatal Quality Collaborative. Am J Perinatol 2016;33(1):9–19. DOI: 10.1055/s-0035-1554794.
48. Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol 2007;31(2):48–55. DOI: 10.1053/j.semperi.2007.02.001.
49. Dinerstein A, Nieto RM, Solana CL, et al. Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants. J Perinatol 2006;26(7):436–442. DOI: 10.1038/sj.jp.7211539.
50. McCallie KR, Lee HC, Mayer O, et al. Improved outcomes with a standardized feeding protocol for very low birth weight infants. J Perinatol 2011;31 Suppl 1:S61–S67. DOI: 10.1038/jp.2010.185.

51. Gephart SM, Hanson CK. Preventing necrotizing enterocolitis with standardized feeding protocols: not only possible, but imperative. Adv Neonatal Care 2013;13(1):48–54. DOI: 10.1097/ANC.0b013e31827ece0a.
52. Patole SK, de Klerk N. Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies. Arch Dis Child Fetal Neonatal Ed 2005;90(2):F147–F151. DOI: 10.1136/adc.2004.059741.
53. Moyses HE, Johnson MJ, Leaf AA, et al. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. Am J Clin Nutr 2013;97(4):816–826. DOI: 10.3945/ajcn.112.042028.
54. Christmann V, Visser R, Engelkes M, et al. Yes, we can–achieve adequate early postnatal growth in preterm infants. Acta Paediatr 2013;102(12):e530. DOI: 10.1111/apa.12302.
55. Thureen PJ, Melara D, Fennessey PV, et al. Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period. Pediatr Res 2003;53(1):24–32. DOI: 10.1203/00006450-200301000-00008.
56. Trivedi A, Sinn JK. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition. Cochrane Database Syst Rev 2013(7):CD008771. DOI: 10.1002/14651858.CD008771.pub2.
57. Vlaardingerbroek H, Vermeulen MJ, Rook D, et al. Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants. J Pediatr 2013;163(3):638–644.e1–5. DOI: 10.1016/j.jpeds.2013.03.059.
58. Sallakh-Niknezhad A, Bashar-Hashemi F, Satarzadeh N, et al. Early versus late trophic feeding in very low birth weight preterm infants. Iran J Pediatr 2012;22(2):171–176. PMID: 23056882.
59. Sisk PM, Lovelady CA, Dillard RG. Effect of education and lactation support on maternal decision to provide human milk for very-low-birth-weight infants. Adv Exp Med Biol 2004;554:307–311. DOI: 10.1007/978-1-4757-4242-8_28.
60. Meier PP, Johnson TJ, Patel AL, et al. Evidence-based methods that promote human milk feeding of preterm infants: an expert review. Clin Perinatol 2017;44(1):1–22. DOI: 10.1016/j.clp.2016.11.005.
61. Spatz DL, Froh EB, Schwarz J, et al. Pump early, pump often: a continuous quality improvement project. J Perinat Educ 2015;24(3):160–170. DOI: 10.1891/1058-1243.24.3.160.
62. Spatz DL. Ten steps for promoting and protecting breastfeeding for vulnerable infants. J Perinat Neonatal Nurs 2004;18(4):385–396. DOI: 10.1097/00005237-200410000-00009.
63. Pineda RG, Foss J, Richards L, et al. Breastfeeding changes for VLBW infants in the NICU following staff education. Neonatal Netw 2009;28(5):311–319. DOI: 10.1891/0730-0832.28.5.311.
64. Cacho NT, Parker LA, Neu J. Necrotizing enterocolitis and human milk feeding: a systematic review. Clin Perinatol 2017;44(1):49–67. DOI: 10.1016/j.clp.2016.11.009.
65. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2018;6:CD002971. DOI: 10.1002/14651858.CD002971.pub3.
66. Taylor SN. Solely human milk diets for preterm infants. Semin Perinatol 2019;43(7):151158. DOI: 10.1053/j.semperi.2019.06.006.
67. Mukhopadhyay K, Narnag A, Mahajan R. Effect of human milk fortification in appropriate for gestation and small for gestation preterm babies: a randomized controlled trial. Indian Pediatr 2007;44(4):286–290. PMID: 17468524.
68. Gathwala G, Shaw C, Shaw P, et al. Human milk fortification and gastric emptying in the preterm neonate. Int J Clin Pract 2008;62(7):1039–1043. DOI: 10.1111/j.1742-1241.2006.01201.x.
69. Di Natale C, Coclite E, Di Ventura L, et al. Fortification of maternal milk for preterm infants. J Matern Fetal Neonatal Med 2011;24 Suppl 1:41–3. DOI: 10.3109/14767058.2011.607569.
70. Arslanoglu S, Boquien CY, King C, et al. Fortification of human milk for preterm infants: update and recommendations of the European Milk Bank Association (EMBA) working group on human milk fortification. Front Pediatr 2019;7:76. DOI: 10.3389/fped.2019.00076.
71. McClave SA, Snider HL. Clinical use of gastric residual volumes as a monitor for patients on enteral tube feeding. JPEN J Parenter Enteral Nutr 2002;26(6 Suppl):S43–S48; discussion S9–S50. DOI: 10.1177/014860710202600607.
72. Parker L, Torrazza RM, Li Y, et al. Aspiration and evaluation of gastric residuals in the neonatal intensive care unit: state of the science. J Perinat Neonatal Nurs 2015;29(1):51–59; quiz E2. DOI: 10.1097/JPN.0000000000000080.
73. Bhatia P, Johnson KJ, Bell EF. Variability of abdominal circumference of premature infants. J Pediatr Surg 1990;25(5):543–544. DOI: 10.1016/0022-3468(90)90569-u.