www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2017;6(2):e060203
doi: 10.7363/060203
Received: 2016 Oct 23; revised: 2017 May 23; accepted: 2017 May 27; published online: 2017 Jun 05

Review

Critical questions on nutrition of preterm infants

Fabio Mosca, Maria Lorella Giannì, Paola Roggero, Camilla Menis, Laura Morlacchi, Nadia Liotto, Beatrice Bracco

Neonatal Intensive Care Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

Abstract

Infants born preterm represent a nutritional emergency that must be addressed immediately in order to avoid/limit the development of nutritional deficits that lead to postnatal growth retardation. When taking care of preterm infants from a nutritional point of view, it must be taken into consideration that promotion of growth is achieved by the accomplishment of their high nutritional needs, that become even more demanding with the occurrence of comorbidities. Identification of the factors that determine and/or affect nutrient requirements is therefore mandatory. A full understanding of the most appropriate biological setting that should be used for establishing preterm infants nutritional requirements is desirable. A deeper knowledge with regard to these points would allow for the provision of appropriate amount of specific essential nutrients, avoiding the under- or overexposure to certain nutrients, and for the individualization of nutritional care of preterm infants.

The avoidance of early malnutrition is of major importance since adequate postnatal growth has been associated with improvement of later neurodevelopment outcome. Limitation of extrauterine growth restriction prevents the need for rapid catch-up growth after discharge which, in turns, has been linked to later adverse metabolic consequences. Increasing evidence has indicated that postnatal growth retardation is accompanied by a fat-free mass deficit, probably related to immature metabolic mechanisms, delayed amino acid administration and protein intakes lower than recommendations. The potential long-lasting effects of these body composition modifications on future health, both in terms of neurodevelopment outcome and metabolic risk, are still under investigation.

Keywords

Preterm infant, macronutrients, human milk, growth, neurodevelopment.

Corresponding author

Fabio Mosca, NICU, Department of Clinical Science and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Via Commenda 12, Milan 20122, Italy; phone +390255032907; fax +390255032429; e-mail: fabio.mosca@unimi.it.

How to cite

Mosca F, Giannì ML, Roggero P, Menis C, Morlacchi L, Liotto N, Bracco B. Critical questions on nutrition of preterm infants. J Pediatr Neonat Individual Med. 2017;6(2):e060203. doi: 10.7363/060203.

Introduction

Neonatologists have focused on optimizing nutritional management of preterm infants that has been recognized as a key contributing factor to the improvement of survival rate and postnatal growth [1]. In terms of developmental programming, targeting the unique nutritional needs of preterm infants is mandatory since the exposure to undernutrition during a critical time window leads to detrimental long-term health consequences [2]. Preterm birth causes the abrupt interruption of maternal-fetal transfer of macro- and micronutrients that preterm infants are unable to synthetize adequately. As a result, infants born preterm represent a nutritional emergency that must be addressed immediately in order to avoid/limit the development of nutritional deficiencies, that lead to postnatal growth retardation, which is still a relatively common finding in neonatal intensive care units [3]. An additional useful tool in monitoring postnatal growth is the newly, longitudinal standards for preterm infants [4]. Accordingly to current recommendations, preterm infants should mimic the growth and body composition of a fetus of the same postmenstrual age and undergo a neurofunctional development similar to that of infants born at term [5]. In order to achieve these goals, several international guidelines on nutritional care of preterm infants are available [6-8]. However, they are mainly based on birth weight rather than on taking into account gestational age, the occurrence of comorbidities and the subsequent need for catch-up growth. It is acknowledged that nutritional requirements of the fetus change throughout pregnancy and, as a result, very preterm infants may present different nutritional needs according to gestational age [9]. The latter implies gaining further insight into the role played by the placenta in modulating the maternal-fetal nutrients passage in addition to the identification of the nutrients that could become conditionally essential for preterm infants due to their developmental immaturity. Notably, the concentration of free amino acids in the placental tissue is higher than in fetal and maternal plasma, suggesting that placenta regulates their flux into the fetal circulation. Long-chain polyunsaturated fatty acids accretion takes place mainly during the third trimester of pregnancy and is targeted towards brain, retina, skeletal muscle and adipose tissue. Consequently, preterm birth is characterized by a decreased adipose store of fatty acids, making the preterm infants dependent on exogenous supply during a critical time period for growth and organ development [10].

Factors contributing to postnatal growth failure

An aggressive nutritional approach has been recommended to limit the nutrients deficit secondary to the abrupt interruption of placental supply and to prevent the occurrence of a catabolic state, particularly in the early postnatal period [11]. However, prescribed and actual nutrient intakes often diverge, leading to cumulative energy and protein deficit [4]. Fear of metabolic intolerance, inadequate parenteral nutrition protocols, need for fluid restriction and feeding intolerance represent the main barriers to the provision of appropriate nutrient intakes [9]. On the other hand, the early provision of a high dose of amino acids has been associated with an increased incidence of electrolyte disturbances [12]. With regard to neurodevelopment and growth, the safety of early high dose of amino acids in the first week of postnatal life has also been questioned [13]. When taking care of preterm infants from a nutritional point of view, it must be taken into consideration that promotion of growth is achieved by the accomplishment of their high nutritional needs. The preterm infant, as he/she switches from intrauterine to extrauterine life, needs to maintain his/her own thermoregulation, fluid balance, and breathing as well as deal with an adverse extrauterine environment that is the neonatal intensive care unit [14]. Accordingly, it has been demonstrated that the resting energy expenditure of preterm infants increases by 140% in the first six weeks of postnatal age whereas that of term infants increases by 47% in the same time frame [15]. However, nutritional needs become even more demanding with the occurrence

of major clinical comorbidities. The need for ventilator support and the development of chronic lung disease rise the energy expenditure by 25% and 20%, respectively [16]. Other conditions, such as sepsis, neurological impairment, cardiac disease and the administration of medications have been reported to affect energy requirements [17]. Consequently, a full understanding of the most appropriate biological setting that should be used for establishing preterm infants nutritional requirements has to be investigated. A deeper knowledge with regard to these points would allow for the provision of appropriate amount of specific essential nutrients, avoiding the under- or overexposure to certain nutrients, and for the individualization of nutritional care.

The efficacy of nutritional intervention relies on the implementation of standardized care protocols and on attention on individual nutritional priorities. Roggero et al. [18] demonstrated that the implementation of nutritional strategies, focused on aggressive parenteral nutrition, adequate weaning from parenteral nutrition and adjustment of enteral nutrients administration improve growth velocity during hospital stay in neonatal intensive care unit, leading to a partial limitation of postnatal growth restriction in a cohort of very low birth weight infants, without any detrimental effect on body composition. Miller et al. [19] demonstrated that the transitional phase from parenteral to enteral nutrition, especially related to decreased intravenous protein intake, may determine a postnatal growth failure. Furthermore, in preterm infants, nutrient requirements differ according to the route of delivery. Specifically, it should be bear in mind that nutrients, particularly proteins, delivered by enteral route, are partially utilized by the splanchnic tissues and, as a result, their systemic availability is limited, negatively affecting growth [20]. Accordingly, Christmann et al. [21] suggested that, even if enteral nutrition can be tolerated, it can fail to prevent the development of nutritional deficits in these vulnerable infants.

Quality of nutrients

Human milk is the first choice for the nutritional support in preterm infants because of its several health benefits on immunological, gastrointestinal and neurodevelopmental functions [22]. When own mothers' human milk is not available or sufficient to guarantee a full supply, donor milk is the best alternative to provide an exclusive human milk diet in very preterm infants [23]. Although donated milk must undergo pasteurization to ensure safety, processing human milk does not entirely abolish its biological activity and many bioactive components are conserved [24]. The number of human milk banks is increasing among neonatal intensive care units worldwide. The implementation of human milk feeding has been associated with improved feeding tolerance, decreased incidence of several comorbidities, such as necrotizing enterocolitis (NEC), sepsis, retinopathy of prematurity (ROP), and optimization of neurodevelopment [1]. Recent studies suggest that the non-nutritive oral administration of colostrum is safe and useful to enhance the development of innate immunity in extremely preterm infants [25].

Human milk fortification

Great amount of evidence indicates that fortification of human milk is required to meet the high preterm infants' nutritional requirements [26, 27]. Several issues have been arisen on the optimal approach to fortification and composition of the fortifiers commercially available. The "adjustable fortification" is based on the metabolic response of the infants [28], whereas the target fortification is based on the analysis of human milk composition. The latter method has been proposed as a safe and feasible strategy, allowing for the provision of adequate individual targeted needs. Morlacchi et al. [26] have assessed growth benefits of targeted fortification during hospital stay in a cohort of very preterm infants compared with standard fortification. The authors reported higher weekly weight gain and daily growth velocity in infants fed targeted fortified human milk in comparison to infants fed standard fortified human milk (**Fig. 1**). Monitoring osmolarity of fortified human milk is necessary to guarantee safe feeds. Within this context, it has to be taken into consideration that carbohydrates are the main responsible for the increase in osmolarity [29]. However, providing energy by means of carbohydrates rather than lipids has been associated with a higher nitrogen balance [30]. The use of human milk-derived fortifiers has been associated with a further decrease of the risk of developing feeding intolerance and NEC. Although the demonstrated benefits associated with an exclusive human milk diet, its implementation is still hindered by the cost of the human milk products [31].

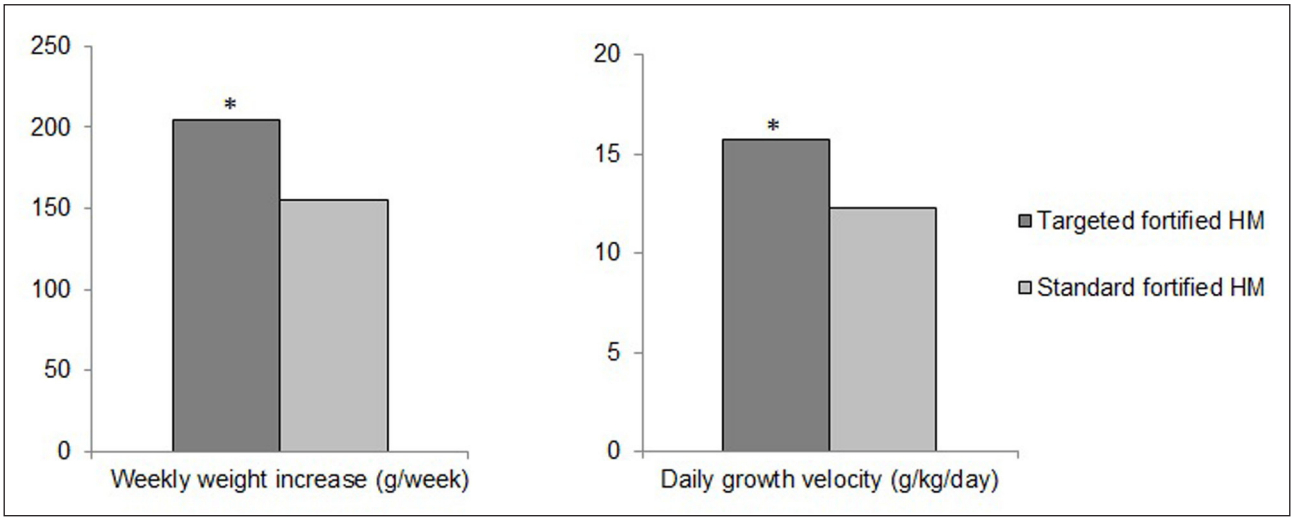

Figure 1. Growth velocity in infants fed targeted fortified human milk (HM) versus infants fed standard fortified human milk (HM). *$p < 0.05$.

Clinical outcomes

Since the development of organ structures and functions takes place during a "preprogrammed" period of life, malnutrition in infancy leads to a profound growth impairment, with long-term consequences on many systemic physiological functions, including the neurobehavioral one (**Fig. 2**). Missing the adequate nutritional supply during a critical time window permanently and negatively affects organogenesis [3].

Among the comorbidities associated with preterm birth, ROP is still a relative frequent event in neonatal intensive care unit, although a more careful control of oxygen supply has been recommended. Of note, increased IGF-1 levels are associated with a decreased risk of developing ROP, suggesting that inadequate nutrition contributes to its occurrence, probably through the impairment of angiogenesis [32]. Stoltz Sjöström et al. [33] demonstrated that the risk of developing severe ROP in a large cohort of extremely preterm was decreased by 24% per each 10 kcal/kg/day increase in energy intake during the first weeks of postnatal life.

Recent evidence focused on the role of human milk in modulating neurological development at medium and long term. Particularly, human milk during hospitalization may lead to a better neurodevelopment at 24 months of corrected age [34]. Belfort et al. [35] have reported that a greater number of days on which infants received > 50% breast milk was associated with a greater deep nuclear gray matter volume at term-equivalent age and with better cognitive and motor performance at 7 years of age.

Increasing evidence indicates that poor postnatal growth, including weight, length and head circumference, in preterm infants is associated with a negative neurodevelopmental outcome. Ehrenkranz et al. [36] showed the relationship between poor weekly growth velocity of head circumference with neurological impairment in extremely low birth weight infants evaluated at 18-22 months of corrected age. Length gain between birth and hospital discharge has been associated with improved performance in the speech domain at 24 months of life in a cohort of very low birth weight infants [37].

Linear growth actually reflects fat-free mass accretion, which, in turns, indicates organ growth and development, in particular the brain. The interrelationship between fat-free mass and neurodevelopment is further supported by the findings that fat-free mass gains during hospital stay have been correlated with improved cognitive and motor scores at 12 months of corrected age [38]. Of note, body composition of preterm infants have been reported to be characterized by a lack of fat-free mass deposition, probably related to immature metabolic mechanisms, delayed amino acid administration and protein intakes lower than recommendations [39]. The different routes macronutrients are supplied during intrauterine life in comparison to postnatal life, in addition to the different environmental conditions preterm infants are exposed to, may also be partially responsible for the development of an altered body composition at term-corrected age. Johnson et al. [39] reported a mean difference in fat-free mass values at term-corrected age of 460 g

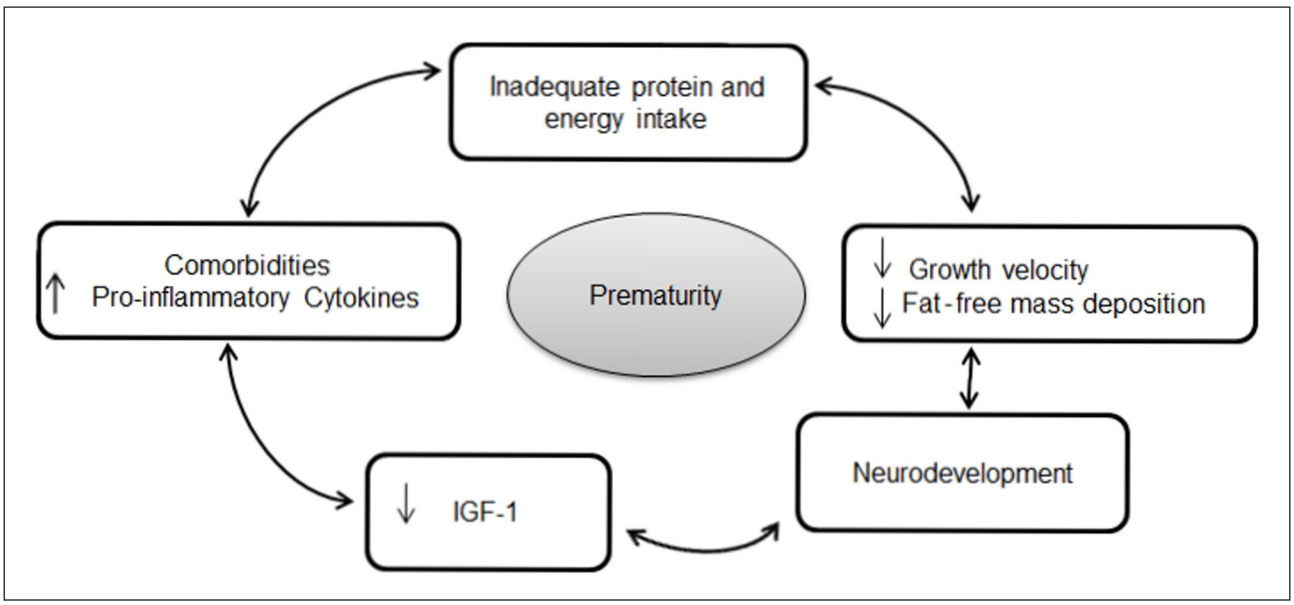

Figure 2. The relationship between nutrition, growth, comorbidities and outcomes following preterm birth.

between preterm and term infants. The potential long-lasting effects of these body composition modifications on future health, both in terms of neurodevelopment outcome and metabolic risk, are still under investigation.

On the basis of the available data, it becomes clear that early promotion of fat-free mass deposition in preterm infants contributes to modulate neurodevelopment in these vulnerable infants. A higher protein-to-caloric ratio, including the provision of fortified human milk, has been demonstrated to be a major contributing factor in increasing fat-free mass deposition. A recent meta-analysis pointed out that formula feeding can negatively affect body composition development from birth to term in preterm infants, being associated with higher fat mass content in comparison with breastfeeding [40].

Conclusions

Providing optimal nutritional care to preterm infants increases survival and enhances quality of life. The implementation of a nutrient-enriched diet during hospital stay promotes growth and optimize neurodevelopmental outcome. The limitation of extrauterine growth restriction prevents the need for rapid catch-up growth after discharge which, in turns, has been linked to later adverse metabolic consequences. In addition, nutritional care after discharge could play a key role in recovering cumulative deficits developed during hospitalization.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Cleminson JS, Zalewski SP, Embleton ND. Nutrition in the preterm infant: what's new? Curr Opin Clin Nutr Metab Care. 2016;19(3):220-5.
2. Chan SH, Johnson MJ, Leaf AA, Vollmer B. Nutrition and neurodevelopmental outcomes in preterm infants: a systematic review. Acta Paediatr. 2016;105(6):587-99.
3. Cooke RJ. Improving growth in preterm infants during initial hospital stay: principles into practice. Arch Dis Child Fetal Neonatal Ed. 2016;101(4):F366-70.
4. Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC, Barros FC, Altman DG, Victora C, Noble JA, Gravett MG, Purwar M, Pang R, Lambert A, Papageorghiou AT, Ochieng R, Jaffer YA, Kennedy SH; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. Lancet Glob Health. 2015;3(11):e681-91.
5. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of low-birth-weight infants. Pediatrics 1985;75(5): 976-86.
6. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R; Parenteral Nutrition Guidelines Working Group; European Society for Clinical Nutrition and Metabolism; European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Society of Paediatric Research (ESPR). Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the

European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41(Suppl 2):S1-87.

7. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, Domellöf M, Embleton ND, Fusch C, Genzel-Boroviczeny O, Goulet O, Kalhan SC, Kolacek S, Koletzko B, Lapillonne A, Mihatsch W, Moreno L, Neu J, Poindexter B, Puntis J, Putet G, Rigo J, Riskin A, Salle B, Sauer P, Shamir R, Szajewska H, Thureen P, Turck D, van Goudoever JB, Ziegler EE; ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85-91.
8. Koletzko B, Poindexter B, Uauy R (Eds.). Nutrition of the preterm infant: Scientific Basis and Practical Guidelines. Basel: Karger, 2014.
9. Brennan AM, Murphy BP, Kiely ME. Optimising preterm nutrition: present and future. Proc Nutr Soc. 2016;75(2):154-61.
10. Robinson DT, Martin CR. Fatty acid requirements for the preterm infant. Semin Fetal Neonatal Med. 2016 Sep 2. [Epub ahead of print].
11. Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol. 2007;31:48-55.
12. Moltu SJ, Strømmen K, Blakstad EW, Almaas AN, Westerberg AC, Brække K, Rønnestad A, Nakstad B, Berg JP, Veierød MB, Haaland K, Iversen PO, Drevon CA. Enhanced feeding in very-low-birth-weight infants may cause electrolyte disturbances and septicemia – a randomized, controlled trial. Clin Nutr. 2013;32:207-12.
13. Blanco CL, Gong AK, Schoolfield J, Green BK, Daniels W, Liechty EA, Ramamurthy R. Impact of early and high amino acid supplementation on ELBW infants at 2 years. J Pediatr Gastroenterol Nutr. 2012;54(5):601-7.
14. Giannì ML, Roggero P, Piemontese P, Orsi A, Amato O, Taroni F, Liotto N, Morlacchi L, Mosca F. Body composition in newborn infants: 5-year experience in an Italian neonatal intensive care unit. Early Hum Dev. 2012;88(Suppl 1):S13-7.
15. Bauer J, Werner C, Gerss J. Metabolic rate analysis of healthy preterm and full-term infants during the first weeks of life. Am J Clin Nutr. 2009;90(6):1517-24.
16. Denne SC. Energy expenditure in infants with pulmonary insufficiency: is there evidence for increased energy needs? J Nutr. 2001;131(3):935S-7S.
17. Bauer J, Hentschel R, Linderkamp O. Effect of sepsis syndrome on neonatal oxygen consumption and energy expenditure. Pediatrics. 2002;110(6):e69.
18. Roggero P, Giannì ML, Orsi A, Amato O, Piemontese P, Liotto N, Morlacchi L, Taroni F, Garavaglia E, Bracco B, Agosti M, Mosca F. Implementation of nutritional strategies decreases postnatal growth restriction in preterm infants. PLoS One. 2012;7(12):e51166.
19. Miller M, Vaidya R, Rastogi D, Bhutada A, Rastogi S. From parenteral to enteral nutrition: a nutrition-based approach for evaluating postnatal growth failure in preterm infants. JPEN J Parenter Enteral Nutr. 2014;38(4):489-97.
20. Corpeleijn WE, Riedijk MA, Zhou Y, Schierbeek H, Huang Y, Chen C, van Goudoever JB. Almost all enteral aspartate is taken up in first-pass metabolism in enterally fed preterm infants. Clin Nutr. 2010;29(3):341-6.
21. Christmann V, Visser R, Engelkes M, de Grauw AM, van Goudoever JB, van Heijst AF. The enigma to achieve normal postnatal growth in preterm infants – using parenteral or enteral nutrition? Acta Paediatr. 2013;102(5):471-9.
22. American Academy of Pediatrics Section on Breastfeeding: Breastfeeding and the use of human milk. Pediatrics. 2012;129:827-41.
23. Senterre T. Practice of enteral nutrition in very low birth weight and extremely low birth weight infants. World Rev Nutr Diet. 2014;110:201-14.
24. O'Connor DL, Ewaschuk JB, Unger S. Human milk pasteurization: benefits and risks. Curr Opin Clin Nutr Metab Care. 2015;18(3):269-75.
25. Lee J, Kim HS, Jung YH, Choi KY, Shin SH, Kim EK, Choi JH. Oropharyngeal colostrum administration in extremely premature infants: an RCT. Pediatrics. 2015;135(2):e357-66.
26. Morlacchi L, Mallardi D, Giannì ML, Roggero P, Amato O, Piemontese P, Consonni D, Mosca F. Is targeted fortification of human breast milk an optimal nutrition strategy for preterm infants? An interventional study. J Transl Med. 2016;14(1):195.
27. Bertino E, Di Nicola P, Giuliani F, Peila C, Cester E, Vassia C, Pirra A, Tonetto P, Coscia A. Benefits of human milk in preterm infant feeding. J Pediatr Neonat Individual Med. 2012;1(1):19-24.
28. Arslanoglu S, Moro GE, Ziegler EE. Adjustable fortification of human milk fed to preterm infants: does it make a difference? J Perinatol. 2006;26:614-21.
29. Choi A, Fusch G, Rochow N, Fusch C. Target Fortification of Breast Milk: Predicting the Final Osmolality of the Feeds. PLoS One. 2016;11(2):e0148941.
30. Kashyap S, Towers HM, Sahni R, Ohira-Kist K, Abildskov K, Schulze KF. Effects of quality of energy on substrate oxidation in enterally fed, low-birth-weight infants. Am J Clin Nutr. 2001;74(3):374-80.
31. Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. J Perinatol. 2016;36(3):216-20.
32. Beardsall K, Vanhaesebrouck S, Frystyk J, Ogilvy-Stuart AL, Vanhole C, van Weissenbruch M, Midgley P, Thio M, Cornette L, Gill B, Ossuetta I, Iglesias I, Theyskens C, de Jong M, Ahluwalia JS, de Zegher F, Dunger DB; NIRTURE Study Group. Relationship between insulin-like growth factor I levels, early insulin treatment, and clinical outcomes of very low birth weight infants. J Pediatr. 2014;164:1038-1044.e1.
33. Stoltz Sjöström E, Lundgren P, Öhlund I, Holmström G, Hellström A, Domellöf M. Low energy intake during the first

4 weeks of life increases the risk for severe retinopathy of prematurity in extremely preterm infants. Arch Dis Child Fetal Neonatal. 2016;101(2):F108-13.

34. Gibertoni D, Corvaglia L, Vandini S, Rucci P, Savini S, Alessandroni R, Sansavini A, Fantini MP, Faldella G. Positive effect of human milk feeding during NICU hospitalization on 24 month neurodevelopment of very low birth weight infants: an Italian cohort study. PLoS One. 2015;10(1):e0116552.
35. Belfort MB, Anderson PJ, Nowak VA, Lee KJ, Molesworth C, Thompson DK, Doyle LW, Inder TE. Breast Milk Feeding, Brain Development, and Neurocognitive Outcomes: A 7-Year Longitudinal Study in Infants Born at Less Than 30 Weeks' Gestation. J Pediatr. 2016;177:133-139.e1.
36. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117:1253e61.
37. Ramel SE, Demerath EW, Gray HL, Younge N, Boys C, Georgieff MK. The relationship of poor linear growth velocity with neonatal illness and two-year neurodevelopment in preterm infants. Neonatology. 2012;102(1):19-24.
38. Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater Early Gains in Fat-Free Mass, but Not Fat Mass, Are Associated with Improved Neurodevelopment at 1 Year Corrected Age for Prematurity in Very Low Birth Weight Preterm Infants. J Pediatr. 2016;173:108-15.
39. Johnson MJ, Wootton SA, Leaf AA, Jackson AA. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. Pediatrics. 2012;130(3): e640-9.
40. Huang P, Zhou J, Yin Y, Jing W, Luo B and Wang J. Effects of breast-feeding compared with formula-feeding on preterm infant body composition: a systematic review and meta-analysis. Br J Nutr. 2016;116(1):132-41.