Early Nutrition and Growth until the Corrected Age of Two Years in Extremely Low Gestational Age Infants

Short title: Early Nutrition and Growth in Preterm Infants

Key words: preterm infant, energy, growth, neonatal nutrition

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Abbreviations

BPD	Bronchopulmonary dysplasia
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SGA	Small for gestational age
TEA	Term-equivalent age

ABSTRACT (221)

Background: Extremely preterm birth is associated with high risk of extra-uterine growth retardation, which has been linked with adverse developmental outcomes.

Objective: We investigated whether nutritional management during the first seven days of life affects growth patterns until the corrected age of two years in extremely preterm infants.

Study Design: A retrospective study of 78 extremely preterm (<28 weeks of gestation) neonates was conducted. Data regarding parenteral and enteral intake of energy, protein, lipids and carbohydrates during the first seven days of life were collected from patient records. The outcome measures included weight, height and head circumference with Z-scores at term-equivalent age and the corrected ages of one and two years. Analyses were performed with hierarchical linear mixed models.

Results: Nutritional intake during the first week of life did not reach the current recommendations. Total intake of energy during the first seven days of life was statistically significantly associated with weight, length and head circumference until the corrected age of two years after adjusting for potential confounding factors. Individual macronutrient intake displayed no association with growth patterns.

Conclusions: Energy intake during the first seven days of life is associated with growth until the corrected age of two years. These results provide support for aggressive early nutritional management of extremely preterm infants.

Introduction

Being born preterm carries a long-term health risk. Preterm infants are at high risk of postnatal growth failure [1] and it is notable that while approximately 20 % of very low birth weight infants suffer from intrauterine growth failure, at the corrected age of 36 weeks growth restriction is observed in approximately 90 %. In addition, the number of infants with growth failure has not been reduced in a manner similar to decreasing mortality and morbidity in preterm children [2]. Greater in-hospital growth is associated with better neurodevelopmental and growth outcomes in extremely low birth weight infants [3]. Nutrition could be one reason for this, and therefore the connection between the early nutrition and later growth and development needs to be carefully studied.

Early postnatal nutrition is one of the components that may influence the infant's growth and cognitive development in the long-term [4]. The catabolic state should be avoided in extremely preterm infants by starting parenteral nutrition shortly after birth, since the newborn infant's own caloric reserves and enteral intake are limited [5][6]. Greater energy and protein intakes in the first week of life are associated with a better developmental outcome at the age of 18 months [7]. Early, aggressive parenteral [8] and enteral [8][9] feeding results in better growth in very low birth weight infants at term-equivalent age, but the more long-term effects of early nutritional management on growth patterns in subjects born extremely preterm are less well known. The purpose of our study was to investigate whether the received nutrition in the first week of life affects the growth of extremely preterm infants until the corrected age of two years.

Materials and methods

The primary study sample consisted of extremely low gestational age (< 28 gestational weeks) infants treated at the Turku University Hospital newborn intensive care unit (NICU) and born between January 2004 and December 2012 (n=155). Only inborn infants were included in the study, out-borns (n=7) were excluded. The exclusion criteria for the study included severe congenital malformations (n=7), death before the age of two years (n=30), infants with incomplete medical records (n=9) and those with growth and developmental follow-ups at some other hospital (n=24). Therefore, the final study sample consisted of 78 preterm infants (Figure 1).

Nutritional data were collected from patient documents used in the Turku University Hospital NICU. Each nutritional day in the NICU begins at 2 PM, and nutritional data were therefore collected from the first incomplete day with the corresponding hours and after that from the following seven complete 24-hour periods. Also, the starting day of enteral nutrition and the total duration of parenteral nutrition was recorded. The individual nutrient composition of human milk was not assessed and therefore estimated concentrations for protein (1.5 g/100 ml), lipids (2.6 g/100 ml) and carbohydrate (6.2 mg/100 ml) were used for calculations regarding human milk as recommended by Cormack et al. [10]. The human milk used was primarily the mother's own milk, added with donor milk to achieve the targeted daily nutritional amounts. None of the infants received preterm formula during the first week of life.

The daily macronutrient data were converted into grams per kilogram per day using the known composition of each nutritional product and the infant's birth weight. In parenteral nutrition, energy content (parenteral protein 4 kcal/g, lipids 10 kcal/g and carbohydrate 3.4 kcal/g) was calculated by each nutrient as recently recommended by Cormack et al [10]. Additionally, total amount of energy was calculated from the collected parenteral nutrition by the macronutrients and from the enteral nutrition by estimating 65 kcal/100 ml for human milk [10].

Background data including the date and time of birth, sex, gestational age, birth weight, height and head circumference with Z-scores, being small for gestational age (SGA, less than -2 SD), maternal antenatal steroids, delivery method, Apgar scores and the umbilical arterial blood pH were collected from the patient records. In addition, major neonatal morbidities including respiratory distress syndrome (RDS), pneumothorax, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), early-onset culture-positive sepsis or meningitis (occurring before the age of three days), late-onset culture-positive bacterial infection or coagulase-negative bacterial infection, fungal infection, cystic periventricular leukomalacia (cystic PVL), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), the need for additional oxygen at the ages of 28 days and 36 gestational weeks, the duration of ventilator treatment, the use of medications including postnatal steroids, indomethacin or ibuprofen, and whether the infant underwent surgery, were recorded. The factors, which were sufficiently prevalent in the population and the most clinically relevant were taken into our final statistical model.

The outcome measures of the study included weight, height and head circumference with their Z-scores at term-equivalent age and the corrected ages of 12 and 24 months. The Z-scores for weight, height and head circumference were recalculated using the new Finnish growth references [11] which are designed and validated specifically for this population. The new Finnish growth charts also include charts for premature-born infants, and they were used in this study to determine the Z-scores.

Numerical data were described as means with range and categorical data as counts and percentages. The mean changes in weight, length and head circumference over two years (expressed as Z-scores) were analyzed using hierarchical linear mixed models for repeated measures (HLMM). The Kenward-Roger correction was used, as well as compounds symmetry covariance structure. Potential confounding factors were tested and statistically significant ones were selected to the final models. Explanatory variables included in the models were energy intake during the first seven days of life, gestational age, SGA, IVH and the age (birth as baseline, term-equivalent age, corrected ages of 12 and 24 months). In addition, interactions between these explanatory variables and age were evaluated in the model to study whether the mean change is different depending on the explanatory variable's value. Pearson correlation (r) was calculated between energy intake and growth factors separately for each age. A similar model was performed in which energy intake was replaced by protein, lipid and carbohydrate intakes. P-values less than 0.05 were considered statistically significant (two-tailed). The statistical analyses were generated using SAS software (version 9.3 for Windows).

Results

The study population consisted of 41 boys and 37 girls with mean gestational age of $26^{2/7}$ weeks (range $23^{3/7}$–$27^{6/7}$ weeks) and mean birth weight of 843 grams (range 530-1320 grams). A more detailed view on clinical characteristics of the study population is presented in Table 1.

The mean intake of energy in the study population was 46.5 kcal/kg/day (ranging from 24.8 kcal/kg/d to 80.7 kcal/kg/d) and did not reach the level of 120 kcal/kg/d currently recommended by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (Table 2). A similar phenomenon was observed with regard to individual macronutrients. It is notable, however, that some of the infants reached the recommended levels of protein and energy intake from the first day. It is also of note that the lipid intake during the first two days of life in the majority of neonates was almost nonexistent.

Modest growth results were observed in the patient population during the first two years of life (Figure 2). There was a statistically significant correlation between first week energy intake and weight at term-equivalent age (r=0.55; p<0.0001) and the corrected ages of 12 (r=0.33; p=0.0028) and 24 months (r=0.25; p=0.0255). Similar associations were observed between early energy intake and height (TEA r=0.57; p<0.0001, 12 months r=0.38; p=0.0007 and 24 months r=0.26; p=0.0191) and head circumference (TEA r=0.57; p<0.0001, 12 months r=0.29; p=0.0100 and 24 months r=0.26; p=0.0234) at the corresponding ages (Figure 3).

After adjusting for potential confounding factors (gestational age, sex, the diagnosis of SGA and IVH), the intake of energy during the first seven days of life was positively associated with weight (HLMM; p=0.0008) and length (HLMM; p=0.0003) as well as head circumference (HLMM;

p=0.0271) from birth until the corrected age of two years (Table 3, see the supplementary table 1 for more detailed data). None of the macronutrients as individual factors were statistically significantly associated with infant weight (for protein p=0.26, for lipids p=0.15 and for carbohydrates p=0.72), length (protein p=0.19, lipids p=0.13 and carbohydrates p=0.77) or head circumference (protein p=0.64, lipids p=0.58 and carbohydrates p=0.68) during the first two years of life.

Discussion

Energy intake during the first seven days of life was correlated with growth until the corrected age of two years in extremely low gestational age infants in this study. Increasing caloric intake has previously been associated with enhanced growth during the first eight weeks of life [12] and an aggressive early nutritional strategy has been shown to improve growth until the age of 40 weeks postmenstrual age [8]. Our data extend these observations. We show that the association of very early nutritional management of extremely preterm neonates with growth patterns extends through the first two years of life.

The total amount of energy had a more significant role than any individual macronutrient in our study population. On the macronutrient level, protein has been shown to positively affect preterm infant growth in some earlier studies [13][14][15] while not in others [16][17]. In addition, enhanced growth outcomes have been reported after administration of both early high protein and high lipid [18]. On the other hand, a high-dose protein nutrition may also be harmful due metabolic consequences [19] and differences between sexes in the amino acid administration and growth have been reported [20].

The infants in this study population did not receive the recommended amounts of energy or macronutrients particularly during the very first days of life. This phenomenon is well recognized, but the situation is gradually improving [21]. The present data were collected from subjects born between the years 2004 and 2012 and, particularly during the first years, nutritional recommendations for preterm infants differed considerably from the present. Accordingly, an increase in average nutrient intake was observed in our subjects over time (Supplementary Table 2).

Our results may be interpreted to suggest that early insufficient nutrition and the ensuing catabolic state impacts the infant's growth trajectory, therefore not reaching its full potential during the first two years of life. Nutritional intake beyond the first week of life was not calculated in this study and it is therefore possible that growth patterns were also affected by later nutrition. It has been previously reported an earlier study that significant variation in the nutritional management of preterm infants has previously been reported to occur during the first week of life [21]. However, all the subjects in the study were treated at the same center with uniform nutritional guidelines for preterm infants both during their stay in the NICU and after discharge. We therefore believe it is safe to assume that the greatest variation in nutritional intake occurred during the first week of life. The reliability of our data is further increased by the fact that the follow-up visits were conducted at the same university hospital, using a standard protocol and are therefore highly comparable. The nutritional data collected were the actual received nutrition, not an estimate. The outcome data collected were elaborate and based on uniform criteria used by the Vermont Oxford Network. This enabled us to control for several confounding factors when analyzing the data. Nonetheless, our relatively small sample size together with the strict exclusion criteria, which may have created a positive bias, may also limit the generalizability of our results.

Our statistical analysis took into account several possible confounding factors. The factors, which were sufficiently prevalent in the population and displayed statistically significant associations in the initial analyses, were taken into our final statistical model. However, even in a standardized situation it was apparent that the most premature and critically ill children received the least nutrition as shown in the first parallel in Figure 3. This may have resulted from limited fluid intake reserved for nutrition after medications and other essential products. On the other hand, it has been suggested that clinicians may be reluctant to provide significant amounts of parenteral nutrition to the most fragile preterm infants [22]. Nonetheless, our statistical model demonstrated that energy intake was an independent factor associated with the children's growth regardless of their illnesses.

Being born small for gestational age was independently associated with growth until the corrected age of two years. The connection between intrauterine growth restriction and later growth is known from earlier studies [23][24][25]. We interpret these data to suggest that intrauterine growth failure may affect early infant growth patterns. It is notable that with intrauterine growth restriction, later over-nutrition and consequent rapid growth is associated with metabolic consequences [26], while under-nutrition [7] and deficient growth [27] with developmental ones. This dilemma calls for more research to understand the determinants of healthy development in this population facing great health risks. Furthermore, our data suggest that, in a similar fashion to intrauterine growth restriction, energy depletion during the first days of life may be unfavorably associated with growth during the first two years of life. Early neurodevelopmental outcomes in our study population would have been of great interest, but due to insufficient resources a full neurocognitive evaluation was not performed to all children.

Our results, together with the previously reported associations between early nutrition, growth and neurodevelopment [28][29][30], underscore the significance of early nutritional management of extremely preterm neonates. Recently, early high content of energy and lipids has been reported to be associated with a lower incidence of brain lesions and better brain maturation at term-equivalent age in preterm neonates [31]. These observations may indicate a more favorable developmental outcome and are consistent with our present data. Nutrition deserves priority in everyday clinical work. More attention should also be given to studying the long-term effects of nutrition. The interconnections between nutrition, growth and neurologic and cognitive development deserve to be assessed in adequately powered prospective clinical trials.

Conclusion

Energy intake during the first seven days of life was independently associated with infant growth until the corrected age of two years in this study. These results provide support for aggressive early nutritional management of extremely preterm infants.

Ethical Statement

Since the study was retrospective and used already existing patient records, it did not cause harm or discomfort to the study subjects. The study was approved by the Department of Pediatrics, Turku University Hospital. All the patient records are handled confidentially and the patients remain anonymous. The study subjects did not directly benefit from the study but it may help treat extremely low gestational age infants better in the future and is thus ethically acceptable.

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References

1 Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al.: Weight Growth Velocity and Postnatal Growth Failure in Infants 501 to 1500 Grams: 2000-2013. Pediatrics 2015;136:e84-92.

2 Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al.: Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196. DOI: 10.1016/j.ajog.2006.09.014

3 Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Kenneth Poole W: Growth in the Neonatal Intensive Care Unit Influences Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants. Pediatrics 2006;117:1253–1261.

4 Cleminson JS, Zalewski SP, Embleton ND: Nutrition in the preterm infant. Curr Opin Clin Nutr Metab Care 2016;19:1.

5 Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R: 1 . 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. J Pediatr Gastroenterol Nutr 2005;3336:1–4.

6 McNelis K, Fu TT, Poindexter B: Nutrition for the Extremely Preterm Infant. Clin Perinatol 2017;44:395–406.

7 Stephens BE, Walden R V, Gargus RA, Tucker R, Mance M, Nye J, et al.: First-Week Protein and Energy Intakes Are Associated With 18-Month Developmental Outcomes in Extremely Low Birth Weight Infants. Pediatrics 2009;123:1337–1343.

8 Dinerstein A, Nieto R, Solana C, Perez G, Otheguy L, Larguia A: Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants. J Perinatol 2006;26:436–442.

9 Maas C, Franz AR, Krogh S von, Arand J, Poets CF: Growth and morbidity of extremely

preterm infants after early full enteral nutrition. Arch Dis Child - Fetal Neonatal Ed 2017;1–3.

10 Comarck BE, Embleton ND, van Goudoever JB, Hay Jr WWJ: Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies. Pediatr Res 2016;79. DOI: 10.1038/pr.2016.26

11 Saari A, Sankilampi U, Hannila M-L, Kiviniemi V, Kesseli K, Dunkel L: New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. Ann Med 2011;43:235–248.

12 Berry MA, Abrahamowicz M, Usher RH: Factors Associated With Growth of Extremely Premature Infants During Initial Hospitalization. Pediatrics 2015;100.

13 Matinolli H-M, Hovi P, Männistö S, Sipola-Leppänen M, Eriksson JG, Mäkitie O, et al.: Early Protein Intake Is Associated with Body Composition and Resting Energy Expenditure in Young Adults Born with Very Low Birth Weight. J Nutr 2015;145:2084–91.

14 Maggio L, Cota F, Gallini F, Lauriola V, Zecca C: Effects of High versus Standard Early Protein Intake on Growth of Extremely Low Birth Weight Infants. J Pediatr Gastroenterol Nutr 2007;44:124–129.

15 Cormack BE, Bloomfield FH: Increased protein intake decreases postnatal growth faltering in ELBW babies. Arch Dis Child Fetal Neonatal Ed 2013;98:F399-404.

16 Bellagamba MP, Carmenati E, D’Ascenzo R, Malatesta M, Spagnoli C, Biagetti C, et al.: One Extra Gram of Protein to Preterm Infants From Birth to 1800 g. J Pediatr Gastroenterol Nutr 2016;62:879–884.

17 Vlaardingerbroek H, Vermeulen MJ, Carnielli VP, Vaz FM, van den Akker CHP, van Goudoever JB: Growth and fatty acid profiles of VLBW infants receiving a multicomponent lipid emulsion from birth. J Pediatr Gastroenterol Nutr 2014;58:417–27.

18 Roelants JA, Vlaardingerbroek H, van den Akker CHP, de Jonge RCJ, van Goudoever JB,

Vermeulen MJ: Two-Year Follow-up of a Randomized Controlled Nutrition Intervention Trial in Very Low-Birth-Weight Infants. JPEN J Parenter Enteral Nutr 2016; DOI: 10.1177/0148607116678196

19 Uthaya S, Liu X, Babalis D, Dore C, Warwick J, Bell J, et al.: Nutritional Evaluation and Optimisation in Neonates (NEON) trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition: a randomised double-blind controlled trial. Effic Mech Eval 2016;3:1–80.

20 Van Den Akker CHP, Te Braake FWJ, Weisglas-Kuperus N, Van Goudoever JB: Observational outcome results following a randomized controlled trial of early amino acid administration in preterm infants. J Pediatr Gastroenterol Nutr 2014;59:714–719.

21 Uthaya S, Modi N: Practical preterm parenteral nutrition: Systematic literature review and recommendations for practice. Early Hum Dev 2014;90:747–753.

22 Embleton ND, Simmer K: Practice of parenteral nutrition in VLBW and ELBW infants. World Rev Nutr Diet 2014;110:177–189.

23 Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol AD: Consensus statement: 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.

24 Kramer MS, Zhang X, Dahhou M, Yang S, Martin RM, Oken E, et al.: Does fetal growth restriction cause later obesity? Pitfalls in analyzing causal mediators as confounders. Am J Epidemiol 2017;185:585–590.

25 Kramer MS, Martin RM, Bogdanovich N, Vilchuk K, Dahhou M, Oken E: Is restricted fetal growth associated with later adiposity ? Observational analysis of a randomized trial 1 – 3 2014;176–181.

26 Sipola-Leppanen M, Kajantie E: Should we assess cardiovascular risk in young adults born

preterm? Curr Opin Lipidol 2015;26:282–287.

27 Mitanchez D, Charkaluk M, Fresson J, Arnaud C: Effect of Intra- and Extrauterine Growth on Long-Term Neurologic Outcomes of Very Preterm Infants. J Pediatr 2016;175:93–9.

28 Leppänen M, Lapinleimu H, Lind A, Matomäki J, Lehtonen L, Haataja L, et al.: Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants. Pediatrics 2014;133:63–70.

29 Harding JE, Cormack BE, Alexander T, Alsweiler JM, Bloomfield FH: Advances in nutrition of the newborn infant. Lancet 2017;389:1660–1668.

30 Su BH: Optimizing nutrition in preterm infants. Pediatr Neonatol 2014;55:5–13.

31 Beauport L, Schneider J, Faouzi M, Hagmann P, Hüppi PS, Tolsa J-F, et al.: Impact of Early Nutritional Intake on Preterm Brain: A Magnetic Resonance Imaging Study. J Pediatr 2016;181:29–36.e1.

FIGURE LEGENDS

Figure 1. Flow chart on final selection of the study population.

Figure 2. Mean growth parameters (Z-scores) at birth, term-equivalent age (TEA) and the corrected ages of 12 and 24 months. Confidence intervals are presented in the accompanying table.

Figure 3. Scatter plots presenting between mean energy intake (x-axis) and weight, length and head circumference (y-axis) at birth, term-equivalent age, corrected ages of 12 and 24 months. P-values are based on Pearson correlation analyses.