Retrospective Review of Postnatal Growth Rate of Premature Infants Receiving Early Parenteral Nutrition in a Malaysian Tertiary Hospital Neonatal Intensive Care Unit

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Abstract

Introduction: Parenteral nutrition (PN) caters for the needs of very low birth weight premature neonates whom the establishment of full enteral nutrition is likely to be delayed. Previous studies demonstrated that early aggressive PN improves neonatal growth parameters. The nutritional goal in premature infants is to achieve postnatal growth rate that is similar to intrauterine foetal growth.
Objective: The objectives of this study were (1) to evaluate the postnatal weight gain rate of low birth weight preterm infants who received early PN, (2) to evaluate the association between co-morbidities in premature infants with weight gain and the correlation between the initiation time and duration of PN with weight gain.
Methods: This was a single centre, retrospective review of premature infants with birth weight less than 1,400 gram receiving PN from January to December 2013. Data were collected from the subjects' medical records. Postnatal weight gain rate from day 7 to day 28 of life was calculated.
Results: The overall median weight gain rate at day 28 was 14.15 gram/kg/day (IQR 6.44), which was slightly below the recommended growth rate of 15 gram/kg/day. The weight gain in neonates with patent ductus arteriosus were significantly lower than their counterparts (median 9.10 gram/kg/day versus 15.03 gram/kg/day, $p<0.01$). The correlation between both initiation time of PN (r_s = -0.141, p = 0.381) and duration of PN (r_s = -0.081, p = 0.613) with weight gain were weak and not statistically significant.
Conclusion: Early PN is a vital nutritional support for neonates to achieve targeted weight gain, overcoming the initial weight drop postnatally, when enteral feeding is not feasible. Nevertheless, the majority of our cohort did not achieve the recommended growth rate despite early initiation of PN. Presence of one or more co-morbidities influences the neonatal weight gain outcome.

Keywords: parenteral nutrition; weight gain; premature neonates

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Introduction

Poor postnatal growth is often observed in preterm infants[1]. Several studies have revealed that preterm infants are often being discharged at a considerably lower percentile of weight, head circumference and length[2-3]. Although the reason for this poor growth can be multifactorial, one of the essential factors is that these infants receive inadequate nutrients at the recommended target, especially early in life[1]. It is very challenging to provide sufficient nutritional intake in preterm infants as they are often unable to tolerate the volume of oral feeds that provide adequate daily requirements for their growth within the first week or two of life. To address this problem, one of the nutritional approaches that was recently advocated was early "aggressive" parenteral nutrition initiation after birth[1,4].

Parenteral nutrition (PN) is the intravenous infusion of all nutrients necessary for metabolic requirement and growth. PN are able to cater for the needs of very low birth weight premature neonates whom the establishment of full enteral nutrition is likely to be delayed. Premature neonates can tolerate PN as early as their first day of postnatal life. Moyses and colleagues[1] have conducted a systematic review and meta-analysis in 2013 to investigate the effect of early PN on the growth outcome in preterm infants and concluded that early PN improves weight gain with no increase in morbidity or mortality.

The ultimate nutritional goal in premature infants is to achieve postnatal growth rate that is similar to intrauterine growth[5]. Foetus grows at a minimum rate of 15g/kg/day during mid-trimester and reduces to 10g/kg/day at term. Uhing and Das[6] had also suggested that the optimal postnatal growth rate for premature infants is to mimic the intrauterine growth velocity which is approximately 16g/kg/day for 23 and 37 weeks' gestation. However, postnatal weight gain in preterm infants is often not attained due to the increased energy requirement associated with under-nutrition, severe illnesses and other co-morbidities[7-8].

Current standard for postnatal nutrition in preterm infants is the one that duplicates normal intrauterine foetal growth rates. In our hospital, the neonatal intensive care unit (NICU) uses the Guidelines of Paediatric Parenteral Nutrition of The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and European Society for Clinical Nutrition and Metabolism (ESPEN) as the standard in prescribing PN for preterm infants. Nevertheless, the outcome of local premature infants receiving PN according to these guidelines has not been reported. Therefore, this study aimed to provide some insight into the outcome of premature infant population who receive early PN in the local setting.

The primary objective of this study was to measure the postnatal weight gain rate of premature infants receiving early PN support within the first 48 hours of life in the NICU. Besides that, this study also evaluated the association between common co-morbidities in premature infants with weight gain and the correlation between the initiation time and duration of PN with weight gain.

Methods

Study Participants

This was a single-centre, retrospective observational review of postnatal growth rate of premature infants receiving early PN in a Malaysian tertiary hospital NICU from 1 January 2013 to 31 December 2013. Inclusion criteria were neonates with very low birth weight of less than 1,400 grams, who received PN that was initiated within 48 hours of life, for a minimum duration of five days. We excluded premature infants with major congenital anomalies, died before day 28 of life, and those who did not have their weight measured on day 7, day 28 and upon discharge.

Data Collection

A standard data collection form was designed to extract information from patient's medical records. Demographic data including birth weight and gestational age at birth were recorded. Other co-

morbidities during hospitalisation including small for gestational age at birth, patent ductus arteriosus, intraventricular haemorrhage (all grades), necrotising enterocolitis and late-onset sepsis or infection were also recorded. Detailed nutritional parameter including total calories and amount of macronutrients provided by PN during the first week of life were documented as well. Initiation time and duration of PN were collected. Subjects' body weight measured at day 7,day 28 and upon discharge using the same electronic digital scales accurate to 10 grams were documented. Time to regain birth weight was also obtained.

Nutritional Management

According to the NICU policy, all new-born infants born with birth weight less than 1,400 grams are initiated with PN as soon as possible, preferably within the first day of life. A standard premixed PN solution bag containing 10% dextrose and 3% amino acid is administrated until the individualised PN solution is available. Fluid intake is restricted to 60 ml/kg/day on day 1, and then advanced by 10-20 ml/kg/day to 150 ml/kg/day at day 7 of life. Enteral feeding is initiated as trophic feeding (<20 ml/kg/day) with breast milk or preterm formula if breast milk is unavailable. When the enteral feeding increases, the amount of PN solution infused is reduced accordingly. PN supplementation is discontinued when enteral feeding achieves 120 ml/kg/day.

Growth Outcomes

The primary outcome of this study was postnatal weight gain rate. Due to the inevitable weight loss in the first week of life and the possibility that the impact of early nutrition on body weight would not be seen until after day 7, weight gain was calculated from day 7 to day 28[5]. The formula for weight gain rate was:

$$\text{weight gain rate (gram/kg/day)} = 1000 \times \frac{(wt_{28} - wt_{7}) / wt_{7}}{28 - 7}$$

wt_{28} - weight on day 28 (kg)
wt_{7} - weight on day 7 (kg)

Time to regain birth weight was also analysed. Our aims of postnatal growth rate and time to regain birth weight were 15 gram/kg/day and 14 days respectively.

Statistical Analysis

We performed all analysis using SPSS software version 16.0. The percentage of infants achieving optimum weight gain of at least 15gram/kg/day on day 28 and the percentage of infants that regained birth weight by day 14 were calculated. Other statistical applications included Man-Whitney U Test was used to analyse the association between common co-morbidities in preterm infants with weight gain and Spearman correlation test was used for the correlation of initiation time and duration of PN with weight gain.

Ethics Statement

This study was registered with the National Medical Research Register (NMRR) (NMRR-15-964-26135) and approved by the Medical Research and Ethics Committee (MREC).

Results

A total of 41 preterm infants were included in our study. Demographic and co-morbidity data of the study population were demonstrated in Table 1 and Table 2. More than a quarter of our cohort (26.8%, n=11) were born small for gestational age. The overall median weight gain at day 28 was 14.15 gram/kg/day (interquartile range (IQR) 6.44), which was slightly below our target of 15 gram/kg/day. Of

the total neonates included for the review, 97.6% (n=40) experienced weight drop to lower than birth weight on day 7 of life. Then, 43.9% (n=18) achieved targeted weight gain of at least 15 g/kg/day while 63.4% (n=26) of the subjects regained their birth weight by day 14. The median duration to regain birth weight was 14 days (IQR 8.00). As high as 87.8% (n=36) of them had extrauterine growth failure which was defined as body weight below the 10th percentile.

Neonates with comorbidities had poorer weight gain. Weight gain in neonates with patent ductus arteriosus were significantly lower compared to the others (median 9.10 g/kg/day versus 15.03 g/kg/day, p <0.01). Otherwise, the impact of other co-morbidities (small for gestational age at birth, intraventricular haemorrhage, necrotising enterocolitis and late-onset sepsis or infection) on postnatal weight gain is not statistically significant (Table 3). With regards to the correlation of initiation time and duration of PN with weight gain, there was a poor negative correlation between initiation time of PN and weight gain at day 28, and it was not statistically significant (r_s = -0.141, p = 0.381) (Figure 1). Similarly, the correlation between duration of PN and weight gain at day 28 was also poor and statistically insignificant (r_s = -0.081, p = 0.613) (Figure 2).

Table 1: Demographic characteristics of the study population (N=41)

Characteristics	n (%)
Gender	
Male	22 (53.7)
Female	19 (46.3)
Ethnicity	
Malay	38 (92.7)
Chinese	1 (2.4)
Indian	1 (2.4)
Others	1 (2.4)
Gestational age (weeks)	
< 28	14 (34.1)
28 – 32	26 (63.4)
> 32	1 (2.4)
Birth weight (grams)	
601 – 800	6 (14.6)
801 – 1,000	14 (34.1)
1,001 – 1,200	19 (46.3)
1,201 – 1,400	2 (4.9)

Table 2: Co-morbidities of the study population (N=41)

Co-morbidity	n
Small for gestational age at birth	11
Intraventricular haemorrhage	12
Necrotising enterocolitis	3
Late onset sepsis / infection	8
Patent ductus arteriosus	10

Table 3: Association between common co-morbidities in preterm infants with growth rate at day 28 (N=41)

Co-morbidity	n	Growth rate, g/kg/day, median (IQR)	*P*-value*
Small for gestational age at birth			0.508
Yes	11	13.88 (6.40)	
No	30	14.50 (7.62)	
Intraventricular haemorrhage			0.352
Yes	12	13.97 (8.94)	
No	29	14.15 (6.21)	
Necrotising enterocolitis			0.617
Yes	3	12.27 (8.82)	
No	38	14.50 (5.99)	
Late onset sepsis / infection			0.402
Yes	8	12.50 (8.82)	
No	33	14.84 (5.82)	
Patent ductus arteriosus			0.009
Yes	10	9.10 (9.82)	
No	31	15.03 (5.98)	

* Mann-Whitney U test

Figure 1: Scatter plot of initiation time of PN and weight gain at day 28

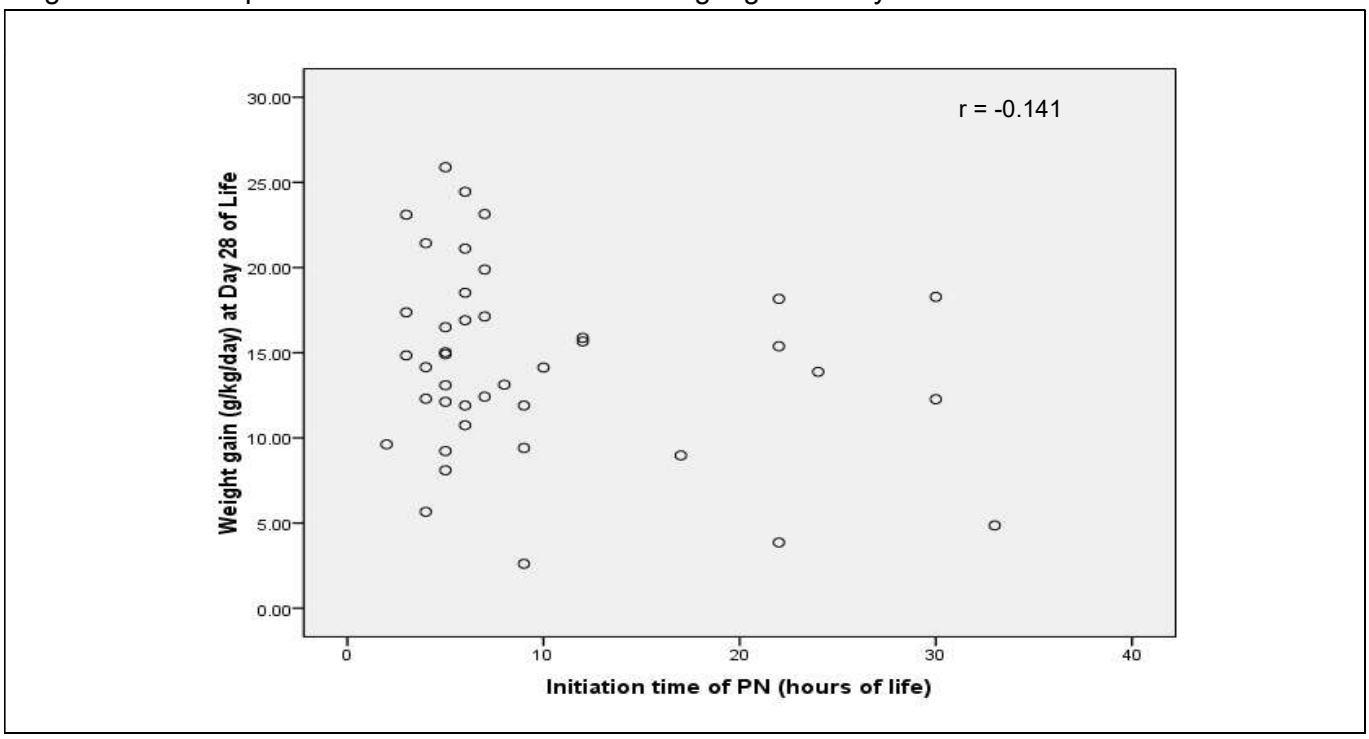
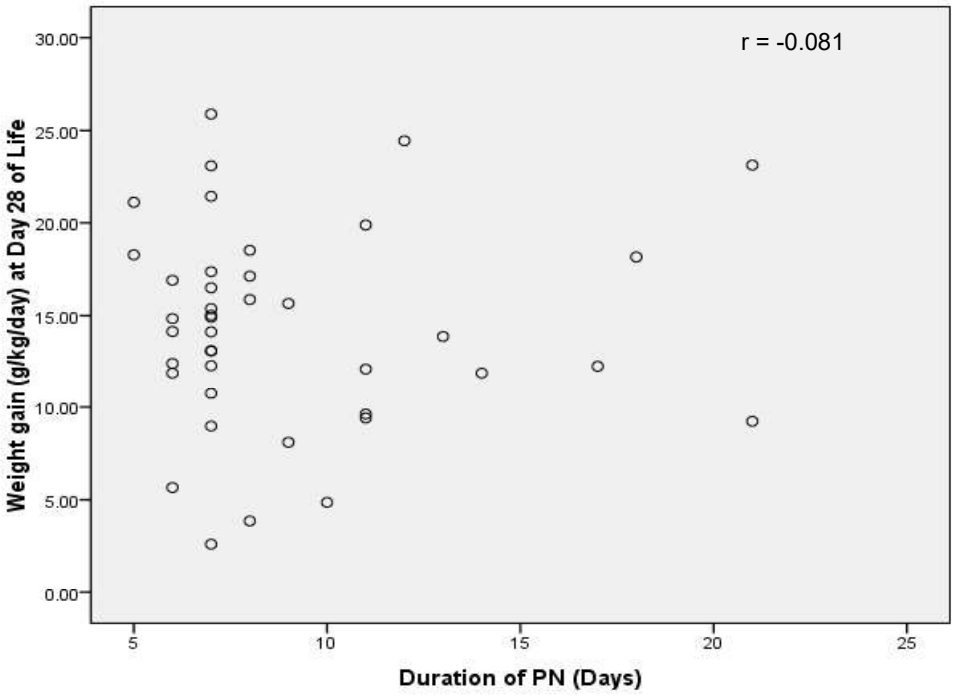


Figure 2: Scatter plot of duration of PN and weight gain at day 28



Discussion

In the early neonatal period of premature infant, PN replaces the role of placenta in ensuring continuous provision of nutrient to the growing neonates[9]. The current standard for postnatal nutrition in preterm infants aims to achieve normal intrauterine foetal growth rates. With regards to the total daily energy provision, the American Academy of Pediatrics (AAP) Committee on Nutrition advocated that energy intake of 50 kcal/kg/day is necessary for basal metabolic function[10]. The postnatal growth is proportional to the provision of energy beyond 50 kcal/kg/day, in which 5 kcal/kg/day is required for every 15gram/kg/day of weight gain. Energy intake can also influence the nitrogen balance and protein accretion is likely to improve with a higher calorie intake[11]. Premature infants require a minimum energy supply of 50 to 60 kcal/kg/day, but 110 to 130 kcal/kg/day is needed to support optimal protein accretion and growth[4,7,11]. Lipid provides additional energy and enables the preterm infants to achieve the target energy requirement faster[12]. Lipid was also administrated to our patients at an initial dose of one gram/kg/day together with glucose and amino acid on the first day of life, which was then increased by one gram/kg/day to the target of three gram/kg/day. Despite the early provision of lipid, our study population only received approximately 35 kcal/kg/day of energy on day 1 with subsequent advancement of 10-15 kcal/kg/day, which was still below the recommended minimum energy intake. This could explain why only 44% (n=18) of our subjects had achieved the targeted weight gain of 15gram/kg/day.

Many literatures agreed that early protein intake may lead to better growth outcomes[11]. Olsen *et al.*[13] proposed that weight gain in premature infants could be raised by 4.1 gram/kg/day with every additional one gram/kg/day of protein. In premature infants, at least one gram/kg/day of amino acid is needed for net protein balance close to zero, while protein accretion will require three gram/kg/day of amino acid[11]. Administration of glucose alone without amino acid can result in 1-2% loss of the total endogenous body protein in extremely low birth weight infants (birth weight < 1,000 gram)[11]. In view of that, provision of amino acid should be started early within 24 hours of birth at 1.5 to 3.0 gram/kg/day

with increment to a target of 3.5 to 4.0 gram/kg/day[5]. Recently, some researchers advocated a higher starting dose of amino acid at 3 gram/kg/day which approximates in utero amino acid flux in animal studies, in the hope of reducing the rate of extrauterine growth failure[14]. While the observational study by Maggio *et al.*[15] has demonstrated better growth outcome in infants receiving higher dose of amino acid supplementation, other controlled trials[9,14,16] have reported that high dose of amino acid did not show benefit on the growth parameters of premature infants. Our policy of amino acid delivery in PN for preterm infants is 3 gram/kg/day on day 1, and then increased to 4 gram/kg/day on day 2 and onwards. However, due to fluid restriction, majority of our cohort has only received 1.5 gram/kg/day of amino acid on day 1 of life and advanced daily at the rate of 1 gram/kg/day to a target dose of 4 gram/kg/day on day 3 or 4, which fell below the recommendation of high dose amino acid.

In previous published studies, postnatal growth rate has been calculated in many different ways using varying starting points (birth weight, nadir, time regained birth weight) and time interval. Lack of standardisation makes the comparison of growth rate between studies difficult. We chose the interval from day 7 to day 28 in our calculation rather than from birth to day 28 with the assumption that the adequacy of the nutritional practice would be better reflected by the weight gain after day 7[5]. Martin *et al.*[5] used the same weight gain calculation for their subjects. Our cohort achieved median weight gain of 14.15 gram/kg/day at day 28, which was lower than the median weight gain of 18.3 gram/kg/day reported in the study by Martin et al[5]. Although these patients received early PN within the first 48 hours of life, the nutritional practice in our centre was not able to meet some of recommendations with regards to total calorie and amino acid intake on the first few days of life. Achieving minimum energy intake of 50-60 kcal/kg/day during the first few days of life can be challenging due to fluid restriction competing against provision of adequate calorie.

The high incidence of extrauterine growth failure at the time of discharge was observed from our cohort and this is consistent with the findings of many other studies[5,17]. Compared to the healthy foetus in utero, premature infants do not have nutritional and growth factor supply from maternal placenta despite their higher energy requirement. Furthermore, weight loss as much as 15% during the first week of life is not accounted for in the intrauterine growth rate. Therefore, postnatal growth failure may be unavoidable as it may not be possible to imitate the intrauterine growth rate, even with the current recommended target postnatal weight gain of 15 gram/kg/day[5].

Previous studies by Ehrenkranz[18] have proposed that premature infants with one or more co-morbidities have poorer growth rate. This is similar to the finding of our study. The energy requirement for those critically ill preterm infants may be even higher than the healthy premature infants[5]. In addition, these severely ill infants sometimes need continuous infusion of other medications such as sedative and inotrope, hence requiring reduction in the infusion rate of PN[9]. In infants with patent ductus arteriosus where one of the conservative management is fluid restriction, achieving adequate calorie intake with the restricted total fluid volume can be very challenging. Hence, it is not surprising that infants with patent ductus arteriosus had a significantly poorer weight gain than their counterparts.

The main limitation of our retrospective study was the use of weight gain as sole indicator in evaluating nutritional adequacy. Growth outcome of our cohort should include other anthropometric measures such as length and head circumstance[5]. Although the height and head circumference was measured weekly in our unit, these data were not utilised for this study as they were not measured by the same operator and hence are subject to bias. Besides that, our subject's body weight was not measured daily during the first postnatal week of life. As the result, the maximum weight loss, which could be another useful growth parameter as described in many other studies, could not be determined in our studies. Thirdly, the types and total calories of enteral feeding from the day of full feeding to day 28 could be a confounding factor affecting our subjects' postnatal weight gain at day 28 of life and upon discharge. This aspect of enteral feeding was not investigated in our study as the detailed data could not be obtained due to its retrospective nature.

Conclusion

Early PN is a vital nutritional support for premature neonates to achieve targeted weight gain and to overcome the initial postnatal weight drop when enteral feeding is not feasible. The majority of our cohort did not achieve the recommended growth rate of 15 gram/kg/day weight gain despite early initiation of PN. The presence of one or more co-morbidities influenced the neonatal weight gain outcome. The major challenge in providing adequate nutritional support during early neonatal period in premature infants was the need for fluid restriction which could limit nutrition delivery.

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Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

Reference

1. Moyses H; Johnson M; Leaf A; Cornelius V. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. *American Journal of Clinical Nutrition*. 2013, 97(4), 816-826.
2. Ehrenkranz R. Early, Aggressive Nutritional Management for Very Low Birth Weight Infants: What Is the Evidence?. *Seminars in Perinatology*. 2007, 31(2), 48-55.
3. Wood N. The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2003,88(6), 492F-500.
4. 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 Paediatric Research (ESPR). *Journal of Pediatric Gastroenterology and Nutrition*. 2005, 41(Supplement 2):S1-S4.
5. Martin C; Brown Y; Ehrenkranz R et al. Nutritional Practices and Growth Velocity in the First Month of Life in Extremely Premature Infants. *PEDIATRICS*. 2009, 124(2), 649-657.
6. Uhing M; Das U. Optimizing Growth in the Preterm Infant. *Clinics in Perinatology*. 2009, 36(1), 165-176.
7. Velaphi S. Nutritional requirements and parenteral nutrition in preterm infants. *S Afr J Clin Nutr*. 2011, 24(3), S27-S31.
8. Hay W. Assessing the effect of disease on nutrition of the preterm infant. *Clinical Biochemistry*. 1996, 29(5), 399-417.
9. Yang S; Lee B; Park H et al. Effect of High vs Standard Early Parenteral Amino Acid Supplementation on the Growth Outcomes in Very Low Birth Weight Infants. *Journal of Parenteral and Enteral Nutrition*. 2012, 37(3), 327-334.
10. American Academy of Pediatrics, Committee on Nutrition. Nutritional needs of low-birth-weight infants. *Pediatrics* 1977, 60, 519-530.
11. Denne S; Poindexter B. Evidence Supporting Early Nutritional Support with Parenteral Amino Acid Infusion. *Seminars in Perinatology*. 2007, 31(2), 56-60.
12. Herrmann K; Herrmann K. Early Parenteral Nutrition and Successful Postnatal Growth of Premature Infants. *Nutrition in Clinical Practice*. 2010, 25(1), 69-75.
13. Olsen I; Richardson D; Schmid C; Ausman L; Dwyer J. Intersite Differences in Weight Growth Velocity of Extremely Premature Infants. *PEDIATRICS*. 2002, 110(6),1125-1132.

14. Clark R; Chace D; Spitzer A. Effects of Two Different Doses of Amino Acid Supplementation on Growth and Blood Amino Acid Levels in Premature Neonates Admitted to the Neonatal Intensive Care Unit: A Randomized, Controlled Trial. *PEDIATRICS*. 2007, 120(6), 1286-1296.
15. Maggio L; Cota F; Gallini F; Lauriola V; Zecca C; Romagnoli C. Effects of High versus Standard Early Protein Intake on Growth of Extremely Low Birth Weight Infants. *Journal of Pediatric Gastroenterology and Nutrition*. 2007, 44(1), 124-129.
16. Burattini I; Bellagamba M; Spagnoli C et al. Targeting 2.5 versus 4 g/kg/day of Amino Acids for Extremely Low Birth Weight Infants: A Randomized Clinical Trial. *The Journal of Pediatrics*. 2013, 163(5), 1278-1282.e1.
17. Clark R; Wagner C; Merritt R et al. Nutrition in the Neonatal Intensive Care Unit: How Do We Reduce the Incidence of Extrauterine Growth Restriction?. *J Perinatol*. 2003, 23(4), 337-344.
18. Ehrenkranz R. Early nutritional support and outcomes in ELBW infants. *Early Human Development*. 2010, 86(1), 21-25.