Professional paper
Stručni članak

ISSN 1848-817X
Coden: MEJAD 53 (2023) 4

The impact of early caloric intake on growth parameters in extremely preterm neonates

Utjecaj ranog kalorijskog unosa na parametre rasta u izrazito nezrele nedonoščadi

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Summary

Introduction: Even though adequate caloric intake is essential for the promotion of growth in extremely premature infants, this is rarely achieved. We investigated how total caloric intake in the first week of life and other events during the hospitalization impact head circumference and weight at 36 weeks of corrected age in extremely preterm infants.

Patients and methods: The study sample consisted of extremely preterm infants treated at Osijek University Hospital Centre, born between January 2018 and December 2020. Records were collected regarding nutritional data, sex, gestational age, birth weight and head circumference, invasive respiratory support, bacterial infection, necrotizing enterocolitis, postnatal steroids, need for supplemental oxygen at 36 weeks gestation, day of introduction of enteral nutrition, duration of parenteral nutrition, length of stay, hemodynamically significant patent ductus arteriosus, cystic periventricular leukomalacia and retinopathy of prematurity.

Results*:* The study cohort included 30 infants. At 36 weeks gestation for weight, median Z scores were -1.63 (IQR -2.34 to -1.15; 95% CI -2.09 to -1.52), and for head circumference were -1.32 (IQR 2.37 to -0.81; 95% CI -1.75 to -0.91). Median energy intake on the first day of life was 33.42 kcal/kg, and 80.78 kcal/kg on day 7. Early caloric intake was not correlated with changes in Z scores for head circumference and weight at 36 weeks of gestation. Other factors influenced changes in head circumference and weight Z scores, namely: gestational age, respiratory support during the first week, need for additional O_2 at 36 weeks, and retinopathy of prematurity requiring intervention.

Conclusion: In our cohort of premature infants at 36 weeks corrected age other factors, not primarily total caloric intake influenced growth parameters.

Key words: Premature Birth, Extremely Premature Infant, Energy Intake, Growth

Sažetak

Uvod: Iako je adekvatan unos kalorija neophodan za poticanje rasta ekstremno nezrele nedonoščadi, on se rijetko postiže. Istraživali smo kako ukupni kalorijski unos u prvom tjednu života, kao i drugi događaji tijekom hospitalizacije utječu na promjenu opsega glave i težine u 36. tjednu korigirane dobi u izrazito nezrele nedonoščadi.

Bolesnici i metode: Uzorak istraživanja činila je izrazito nezrela nedonoščad koja je liječena u Kliničkom bolničkom centru Osijek, a rođena su od siječnja 2018. do prosinca 2020.godine. Prikupljeni su podaci o kalorijskom unosu, spolu, gestacijskoj dobi, porođajnoj težini, opsegu glave, invazivnoj respiratornoj potpori, bakterijskim infekcijama, nekrotizirajućem enterokolitisu, primjeni postnatalnih steroida, potrebi za dodatnim kisikom u 36. tjednu gestacije, vremenu vođenja enteralne prehrane, trajanju

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Received/*Primljeno* 2023-10-09; Revised/*Ispravljeno* 2023-10-25; Accepted/*Prihvaćeno* 2023-11-16

parenteralne prehrane, duljini boravka, postojanju hemodinamski značajanog ductus arteriosus-a, cističnoj periventrikularnoj leukomalaciji i retinopatiji nedonoščadi.

Rezultati: Studijska kohorta uključivala je 30 izrazito nezrele nedonoščadi. U 36. tjednu trudnoće za težinu, medijan Z skora je bio -1,63 (IQR -2,34 do -1,15; 95% CI -2,09 do -1,52), a za opseg glave bio je -1,32 (IQR 2,37 do -0,81; 95% CI -1,75 do -0,91). Medijan energetskog unosa prvog dana života iznosio je 33,42 kcal/kg, a 7. dana 80,78 kcal/kg. Rani unos kalorija nije bio u korelaciji s promjenama u Z rezultatima za opseg glave i težinu u 36. tjednu gestacije. Na promjene u Z rezultatima opsega glave i težine utjecalis u drugi čimbenici: gestacijska dob, respiratorna podrška tijekom prvog tjedna, potreba za dodatnim O_2 u 36. tjednu i retinopatija nedonoščadi koja zahtijeva intervenciju.

Zaključak: U kohorti izrazito nezrele nedonoščadi, u korigiranoj dobi od 36 tjedana, drugi čimbenici, a ne primarno ukupni kalorijski unos, utjecali su na parametre rasta.

Ključne riječi: Prijevremeni porod, izrazito nezrela nedonoščad, energetski unos, rast

Med Jad 2023;53(4):263-270

Introduction

Head circumference and weight are routinely measured during the course of treatment of premature infants. Weight is usually measured every 24 or 12 hours and head circumference is usually measured on a weekly basis. This data provides valuable short term insights into the premature infants' clinical condition and has been used as a predictor of total cerebral volume and neurological outcomes.[1]

Weight gain changes[2] and head circumference trajectory during the initial neonatal intensive care unit (NICU) hospitalization, independently of each other have shown to reflect neurodevelopmental outcomes.[3] Even though adequate caloric intake is essential for promotion of growth in extremely premature infants, this is rarely achieved due to a variety of reasons (overall poor state of the neonate, abdominal distension due to CPAP administration, hyperglycemia, gut ischemia, hyperlipidemia, high blood urea concentration).[4]

The stated goal in providing adequate caloric and micronutrient intake in extremely premature infants is to meet the growth rate of the healthy fetus of the same gestational age.[5] However, in most cases of extreme prematurity it takes up to 17 days for the preterm infant to regain birth weight.[6]

At the corrected age of 36 weeks gestation, approximately 90% of extremely preterm infants suffer from growth restriction.[7] Better growth until discharge in very preterm infants is associated with reduced incidence of bronchopulmonary dysplasia (BPD)[8], reduced risk for severe retinopathy of prematurity (ROP)[9], better brain growth[10] and better neurodevelopmental and growth outcomes.[11]

The purpose of our study was to investigate how total caloric intake in the first week of life and other conditions during the hospitalization impact head circumference and weight at 36 weeks of corrected age.

Patients and methods

This study included all extremely low gestational age (<28 gestational weeks) infants treated and discharged from the Osijek University Hospital Centre, born between January 2018 and December 2020 (n = 30). Only inborn infants were included in the study. The exclusion criteria for the study included death before 36 weeks gestation, hypertensive hydrocephalus, and severe congenital malformation. The final sample consisted of 30 extremely preterm infants. Data regarding nutrition was gathered from the patient's records.

Daily nutritional data was collected from the first incomplete day (on an hourly basis) and after then for the next 6-24 hour days. The estimation of nutrient composition in human milk was as follows: 1.5 g/100 mL for protein, 2.6 g/100 mL for lipids, and 6.2 mg/100 mL for carbohydrates, as per Cormack et al.[12] For infants who were given preterm formula within the first week of life, energy and nutritional calculations were determined based on the disclaimers provided by the manufacturer of the preterm formula.

For parenteral nutrition, the energy content was calculated using the recommended values provided by Cormack et al.[12]: 4 kcal/g for parenteral protein, 10 kcal/g for lipids, and 3.4 kcal/g for carbohydrates. In previous studies, breast milk was estimated to contain 65 kcal/100 ml.[7]

Supplementary data were obtained from the patient records, encompassing information such as the date and time of birth, gender, gestational age, birth weight, head circumference with Z scores, instances of invasive respiratory support within the first week of life, and the presence of early bacterial infection, necrotizing enterocolitis requiring surgery, postnatal steroids for prevention of BPD, need for supplemental oxygen at 36 weeks gestation, day of introduction of enteral nutrition, total duration of

parenteral nutrition, length of hospital stay, hemodynamically significant patent ductus arteriosus (PDA), presence of cystic periventricular leukomalacia and retinopathy of prematurity requiring intervention.

The study outcomes comprised the weight and head circumference, along with their respective Z scores, measured at 36 weeks gestation. These Z scores were calculated using the Fenton growth charts specifically designed for preterm infants.[13]

Investigation of this data set was approved as a part of doctoral dissertation by Osijek University Hospital Centre and Faculty of Medicine, University J. J. Strossmayer Osijek Ethics Committee No. 2158-61-07-19-51. Research carried out is in compliance with Helsinki Declaration.

Statistical analysis

Descriptive statistical methods were employed to describe the data. The association between variables that did not follow a normal distribution was assessed using the Spearman's rho test. Linear regression was utilized to identify significant predictors in predicting Z-score Weight and head circumference. A significance level of 0.05 (Alpha) was set. The statistical analysis was conducted using MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

Results

The final cohort consisted of 30 extremely preterm neonates. The clinical characteristics of the study population are shown in Table 1.

The median energy intake on the first day of life (DOL) was 33.42 kcal/kg, which progressively increased to 80.78 kcal/kg by DOL 7. The average energy intake during the first week of life is presented in Table 2.

At birth, the median Z scores for weight were 0.13 (IQR -0.31 to 0.86; 95% CI -0.20 to 0.46) and for head circumference were -0.14 (IQR -0.94 to 0.50; 95% CI -0.43 to 0.34). At 36 weeks gestation for weight, median Z scores were -1.63 (IQR -2.34 to -1.15; 95% CI -2.09 to -1.52), and for head circumference were -1.32 (IQR 2.37 to -0.81; 95% CI -1.75 to -0.91). This is shown in Figure 1.

We analyzed the correlation of different factors and changes in head circumference and weight Z scores at 36 weeks gestation. For weight changes the only significant correlation was with gestational age, while for changes in head circumference Z scores were correlated with gestational age, any respiratory support during the first week, the need for additional O_2 at 36 weeks, and retinopathy of prematurity requiring intervention. This is shown in Table 3.

A linear regression (bivariate regression) analysis was done to determine the impact of each of the factors examined on the variation in Z scores in head circumference and weight at 36 weeks gestation. The sole factor influencing changes in weight at 36 weeks gestation was gestational age, while regarding changes in Z scores in head circumference were gestational age, need for supplemental oxygen, birth weight, invasive respiratory support during the first week of life and NEC requiring surgery. No significant correlation was observed between energy intake during the first week of life and changes in Z scores, as indicated in Table 4.

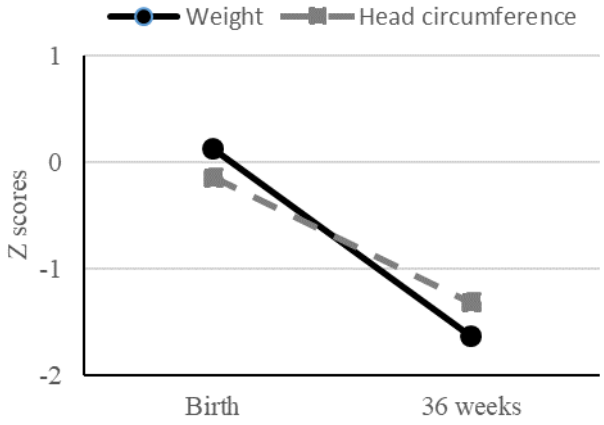

Figure 1 Changes in weight and head circumference from birth to 36 weeks gestation corrected age

Slika 1. Promjene u težini i opsegu glave od rođenja do 36 tjedana korigirane dobi

Discussion

The objective of this study was to examine the potential significance of early caloric intake during the first week of life in extremely premature infants on growth parameters at 36 weeks of corrected gestational age. Additionally, the study aimed to analyze the influence of other factors and their impact on these growth parameters.

Meeting the optimal caloric intake during the initial weeks of life for extremely premature infants is often challenging.[14] This difficulty arises from the fact that nutritional support for these infants, until they can establish full enteral feeds, relies on parenteral nutrition.[15] According to published guidelines, it is recommended to achieve full enteral feeds within 7 days for infants weighing between 1–1.5 kg and within 14 days for infants weighing less than 1 kg.[16] However, in this study population, the infants did not receive the recommended energy

amounts during the first week of life, as suggested by the guidelines (Table 2).

These findings align with similar results reported in other studies.[7]

Table 1 Clinical characteristics of the study population
Tablica 1. Kliničke karakteristike ispitivane populacije

Clinical characteristics/*Kliničke karakteristike*	
Sex, female (n %) *Spol, žensko*	14 (47)
Completed gestational age (Median (IQR*) *Završena gestacijska dob*	26 (25 – 27)
Birth weight (g) (Median IQR*) *Težina pri porodu*	0.872 (0.704 – 0.992)
Any invasive respiratory support during the first week (n (%) *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*	22 (73)
Early bacterial infection (n (%)) *Rana bakterijska infekcija*	11 (37)
NEC† requiring surgery (n (%) NEC†*koje traži kirurški zahvat*	4 (13)
Postnatal steroids (n (%) *Postanatalni steroidi*	9 (30)
O_2 at 36 weeks gestation (n (%) *O_2 u 36. tjednu trudnoće*	6 (20)
Day enteral nutrition started (Median (IQR*) *Započela dnevna enteralna prehrana*	2 (2 – 3)
The total duration of parenteral nutrition, days (Median (IQR*) *Ukupno trajanje parenteralne prehrane, dana*	30 (20 – 43)
Length of stay, days (Median (IQR*) *Duljina trajnja, dani*	77 (68 – 103)
Hemodynamically significant PDA (n (%) *Hemodinamski značajan PDA*	7 (23)
cPVL‡ (n (%))	2 (7)
ROP§ requiring intervention (n (%) ROP§ *koji zahtjeva intervenciju*	15 (50)

*IQR, interquartile range/*interkvartilni raspon*; †necrotizing enterocolitis/ *nekrotizirajući enterokolitis*, ‡cystic periventricular leucomalatia/ *cistična periventrikularna leukomalacija*; §ROP, retinopathy of prematurity/ *retinopatija nedonoščadi*

Table 2 Daily average energy intake during the first week
Tablica 2. Dnevni prosječni energetski unos tijekom prvog tjedna

Day of life/*dan života*	**Energy/*energija*, kcal/kg (Median (IQR*))**
1	33.42 (27.33 - 41.46)
2	57.68 (51.02 - 65.04)
3	65.54 (57.61 - 75.31)
4	70 (61.08 - 80.01)
5	73.71 (63.4 - 88.1)
6	79.08 (63.97 - 92.68)
7	80.78 (70.49 - 103.66)
Total per day, median (IQR*) *Sveukupno po danu*	67.25 (59.22 – 75.21)

*IQR, interquartile range/*interkvartilni raspon*

Table 3 Correlation of different factors and changes in head circumference and weight Z scores at 36 weeks gestation
Tablica 3. Korelacija različitih čimbenika i promjena u Z vrijednostima opsega glave i težine u 36. tjednu korigirane dobi

	Spearman Rho (P value) / *P vrijednost*	
Factor	**Change in head circumference Z score at 36 weeks** ***Promjena u Z rezultatu opsega glave u 36. tjednu***	**Change in weight Z score at 36 weeks** ***Promjena Z rezultata u težini nakon 36 tjedana***
Sex, female *Spol, žensko*	-0.278 (0.14)	0.139 (0.46)
Completed gestational age *Završena gestacijska dob*	0.526 (0.003)	0.383 (0.04)
Any invasive respiratory support during the first week *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*	-0.435 (0.02)	-0.209 (0.27)
Early bacterial infection *Rana bakterijska infekcija*	0.040 (0.83)	0.188 (0.32)
NEC* requiring surgery *NEC* koji zahtijeva kirurški zahvat*	-0.329 (0.08)	-0.136 (0.47)
Postnatal steroids *Postnatalni steroidi*	-0.332 (0.07)	0.130 (0.49)
O_2 at 36 weeks gestation *O_2 u 36. tjednu trudnoće*	-0.568 (0.001)	0.067 (0.72)
Day enteral nutrition started *Dan početka dnevne enteralne prehrane*	-0.177 (0.35)	0.090 (0.64)
PDA†	-0.219 (0.25)	-0.105 (0.58)
cPVL‡	-0.108 (0.57)	-0.232 (0.22)
ROP§ requiring therapy *ROP§ koji zahtijeva intervenciju*	-0.431 (0.02)	-0.089 (0.64)
Energy (kcal/kg) in the first 7 days *Energija kcal/kg kod prvih 7 dana*	0.291 (0.12)	0.154 (0.42)

*NEC, necrotizing enterocolitis, †PDA, patent ductus arteriosus, ‡cPVL, cystic periventricular leucomalatia; §ROP, retinopathy of prematurity
NEC, nekrotizirajući enterokolitis, †PDA, otvoreni ductus arteriosus, ‡cPVL, cistična periventrikularna leukomalacija; §ROP, retinopatija nedonoščadi

Table 4 Linear regression analysis of factors influencing changes in head circumference and weight Z scores
Tablica 4. Linearna regresijska analiza čimbenika koji utječu na promjene u Z vrijednostima opsega glave i težine

Risk Factor/*Faktor rizika*	**ß**	**95% CI**	**R2**	**P value**
Weight Z score changes / *Promjene u Z rezultatu težine*				
Sex, female /*spol, žensko*	0.18	-0.36 to 0.71	0.016	0.5
Completed gestational age *Završena gestacijska dob*	0.22	0.01 to 0.43	0.143	0.04
Any invasive respiratory support during the first week *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*	-0.31	-0.91 to 0.29	0.038	0.3
Early bacterial infection *Rana bakterijska infekcija*	0.31	-0.24 to 0.85	0.045	0.26
NEC* requiring surgery *NEC* koji zahtijeva kirurški zahvat*	-0.24	-1.03 to 0.55	0.014	0.54
Postnatal steroids *Postnatalni steroidi*	0.23	-0.35 to 0.81	0.023	0.42

Risk Factor/*Faktor rizika*	**ß**	**95% CI**	**R2**	**P value**
O_2 at 36 weeks gestation *O2 u 36. tjednu trudnoće*	0.12	-0.55 to 0.79	0.005	0.71
Day enteral nutrition started *Dan početka dnevne enteralne prehrane*	0.07	-0.13 to 0.27	0.017	0.49
Hemodynamically significant PDA† *Hemodinamski značajan PDA†*	-0.17	-0.81 to 0.46	0.011	0.58
cPVL‡	-0.63	-1.69 to 0.42	0.051	0.23
ROP§ requiring intervention *ROP§ koji zahtijeva intervenciju*	-0.09	-0.64 to 0.44	0.005	0.71
Energy kcal/kg (sum 7 days) *Energija kcal/kg (zbroj 7 dana)*	0.001	-0.002 to 0.005	0.017	0.49
Head circumference Z score changes / *Opseg glave Z rezultat se mijenja*				
Sex, female /*spol, žensko*	-0,55	-1.26 to 0.16	0.082	0.13
Completed gestational age *Završena gestacijska dob*		0.22 to 0.72	0.348	<0.001
Any invasive respiratory support during the first week *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*		-1.63 to -0.09	0.158	0.03
Early bacterial infection *Rana bakterijska infekcija*		-0.57 to 0.96	0.010	0.6
Birth weight *Težina pri porodu*	2,78	1.16 to 4.42	0.304	0.002
NEC* requiring surgery *NEC* koji zahtijeva kirurški zahvat*	-1,07	-2.08 to -0.06	0.145	0.04
Postnatal steroids *Postnatalni steroidi*	-0,64	-1.41 to 0.13	0.093	0.1
O_2 at 36 weeks gestation *O2 u 36. tjednu trudnoće*	-1,35	-2.11 to -0.58	0.316	0.001
Day enteral nutrition started *Dan početka dnevne enteralne prehrane*	-0,18	-0.46 to 0.09	0.064	0.18
Hemodynamically significant PDA† *Hemodinamski značajan PDA†*	-0,61	-1.45 to 0.24	0.072	0.15
cPVL‡	-0,25	-1.74 to 1.23	0.004	0.73
ROP§ requiring intervention *ROP§ koji zahtijeva intervenciju*	-0,78	-1.46 to -0.09	0.165	0.03
Energy kcal/kg (sum 7 days) *Energija kcal/kg (zbroj 7 dana)*	0,004	-0.001 to 0.01	0.102	0.09

*NEC, necrotizing enterocolitis, †PDA, patent ductus arteriosus, ‡cPVL, cystic periventricular leucomalatia; §ROP, retinopathy of prematurity

NEC, nekrotizirajući enterokolitis, †PDA, otvoreni ductus arteriosus, ‡cPVL, cistična periventrikularna leukomalacija; §ROP, retinopatija nedonoščadi

Recently, the traditional belief that extremely premature neonates should exhibit growth patterns similar to those of fetuses has been challenged. Despite implementing optimal clinical practices, a majority of extremely premature infants still experience extrauterine growth retardation. It is important to recognize that attaining fetal growth rates may not be realistic or appropriate for these infants, and that individualized growth trajectories should be considered to optimize their overall health and development.[17]

All 30 extremely premature infants in our cohort exhibited negative changes in Z scores for head circumference and weight at 36 weeks gestation (Figure 1). The observation that extremely premature infants experience extrauterine growth retardation is a recognized phenomenon supported by previous studies.[7,18] However, it is important to note that this initial growth delay is often followed by a period of catch-up growth. Catch-up growth typically begins in early infancy and typically concludes around 2-3 years of age, although in certain cases, it may extend into adolescence.[19]. During this catch-up growth phase, the premature infants show an accelerated growth rate, aiming to bridge the gap between their current growth status and the growth trajectory expected for their age. Monitoring and promoting appropriate catch-up growth are crucial for

optimizing the long-term health and development of extremely premature infants.

Subsequently, we conducted an analysis to examine the correlation between early caloric intake during the first weeks of life and other factors that could potentially influence the growth parameters in our cohort of extremely premature infants (Table 3). Interestingly, we did not find a significant correlation between total caloric intake during the first week of life and changes in Z scores for head circumference and weight at 36 weeks of gestation.

It is worth noting that other studies have examined growth patterns over longer periods, including until discharge or follow-ups of 1 to 3 years.[7,20-23] While our study did not specifically evaluate early caloric intake as a potential risk factor for long term postnatal growth, these other studies have considered various factors associated with achieving adequate caloric intake, and they have shown positive correlations with postnatal growth outcomes.

For instance, Lee et al found that the duration of total parenteral nutrition and the number of days required to reach enteral nutrition above 100 cc/kg were significantly associated with postnatal growth retardation.[20] Additionally, Kavurt et al identified that the time taken to regain birth weight was a risk factor for postnatal growth restriction in preterm infants.[23] A study by Hiltunen et al found a positive. association between energy intake during the first 7 days of life and weight, length, and head circumference from birth until the corrected age of 2 years.[7]

While our study did not observe a direct correlation between early caloric intake and growth parameters at 36 weeks of gestation, it is essential to consider that achieving adequate caloric intake and other related factors may still play a role in postnatal growth outcomes in the longer term.

For changes in weight Z scores at 36 weeks the only significant positive correlation was found for completed gestational age ($p = 0.04$), while for changes in head circumference Z scores a significant positive correlation was found for completed gestational age ($p = 0.003$), while a negative correlation was found in infants that received any invasive respiratory support during the first week ($p = 0.02$), and in those which had a need for additional O_2 at 36 weeks ($p = 0.001$) and those which developed retinopathy of prematurity requiring intervention ($p = 0.02$). These findings are reported by other researchers, they found that the severity of respiratory disease has a high impact on postnatal growth failure.[20-24]

In the linear regression analysis of factors influencing changes in head circumference Z scores additional factors were found to be significant, namely NEC requiring surgery ($p = 0.04$) and ROP requiring intervention ($p = 0.03$). This is also a finding reported earlier.[19,20]

Our study has several limitations. First, we analyze a relatively small number of patients. Second, we focused only on the impact on growth measurements until 36 weeks of corrected age. Several previous studies with long-term follow-up provide similar results, but only a small number of them provided some results regarding growth until term equivalent age.[7]

In conclusion, in our cohort of extremely premature infants, at 36 weeks corrected age, other factors, not primarily total caloric intake, influenced growth parameters, especially head circumference growth. However, this conclusion is not straightforward since respiratory problems, the infant's more severe general condition, and complications during hospitalization contributed to increased caloric requirements in extremely immature premature infants.

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