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Original article

The catch-up growth at 2 years of newborns born less than 32 weeks of gestational age

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Abstract

Introduction: Very low birth weight newborns have an increased risk of neonatal complications and long-term malnutrition. In this paper the authors try to evaluate the catch-up growth of infants born with less than 32 weeks of gestational age (GA) and the effect of breast milk during the neonatal period on the later nutritional status, reflected on the somatometry at the age of 2.

Material and methods: This is a retrospective study with a population of newborns with GA less than 32 weeks or weighing less than 1,500 grams, admitted to a level III Neonatal Intensive Care Unit between 2009 and 2012. Patients are divided into two groups: group 1, children with follow-up at 2 years of age; group 2, follow-up drop-out. Statistical analysis was performed using SPSS®, p-values < 0.05 were considered statistically significant.

Results: 262 newborns were included, 158 (60.3%) had a clinical follow-up at 2 years-old. We found statistically significant differences between the two groups, regarding lower GA and head circumference z-score at birth, as well as increased risk of infection in group 1; comorbidities were more frequent in group 2. Birth weight z-score is the only variable that positively affects weight z-score. Follow-up weight z-score is positively affected by weight z-score at birth and negatively affected by the extent of in-hospital exclusive enteral feeding. GA and age at onset of exclusive enteral feeding do not present significant correlation.

Intraperiventricular haemorrhage is associated with lower head circumference z-score at follow-up; in contrast, larger head circumference z-score at discharge and weight z-score at follow-up are associated with larger head circumference at follow-up.

Conclusion: This study highlights how a deficient nutritional status at discharge delays a growth recovery at the age of 2, emphasizing the influence of birth weight and breast milk on growth.

Keywords

Very low birth weight, prematurity, z-score, growth, nutrition, breast milk.

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Introduction

In this paper the authors try to evaluate the catch-up growth of infants born before 32 weeks of gestational age (GA) and the effect of breast milk during the neonatal period on the later nutritional status, reflected on the somatometry at 2 years of age.

The group of newborns is heterogeneous, includes preterm infants weighing 1,500 grams or less, infants with a weight that is normal for GA (adequate for gestational age [AGA]) and others with intrauterine growth restriction (IUGR) [1]. Nevertheless, this group is especially vulnerable to neonatal complications and presents a high risk of sequelae and long-term malnutrition [2].

Anthropometry is the method used to evaluate the growth of preterm newborns [3]. Weight gain, head circumference and linear growth have implications in long-term outcomes in preterm infants [4].

We know that premature infants have a high risk of reducing or interrupting enteral feeding. These factors may negatively influence the recovery of birth weight and the rate of weight gain. After birth, several external factors can cause weight loss and influence the recovery of birth weight, resulting in malnutrition at discharge [5].

The American Academy of Pediatrics (AAP) recommends that the preterm infant should grow similarly to a fetus at the same GA, so adequate growth and development of preterm infants depend on adequate nutrition that ideally seeks to mimic the uterine environment [6, 7]. The AAP also recommends that all preterm infants should be fed with human milk (including very low birth weight infants) [7, 8].

Material and methods

This is a retrospective study that involves a population of newborns with GA less than 32 weeks or weighing less than 1,500 grams, included in the Very Low Birth Weight National Database (VLBWND), admitted to a level III Neonatal Intensive Care Unit (NICU) between 2009 and 2012. Children with missing data (n = 24) or death (n = 62) were excluded.

The VLBWND began in Portugal in 1994; it currently includes all newborns weighing 1,500 g or less, newborns with GA less than 32 weeks, regardless of birth weight, and twins (regardless of weight and GA) [9].

Patients are divided into two groups: group 1, children with follow-up at 2 years of age; group 2, follow-up drop-out.

The anthropometric measurements, weight, length and head circumference z-scores were calculated using the Fenton curves at birth and discharge [10]; the World Health Organization (WHO) curves were used at follow-up (between 24- and 36-months corrected age) [11].

The comorbidities analysed for each group included persistent ductus arteriosus (PDA), infection (late sepsis or meningitis), necrotizing enterocolitis (NEC), intraperiventricular haemorrhage greater than or equal to 3 or infarction and bronchopulmonary dysplasia.

Statistical analysis was performed using the IBM-SPSS® software, with a 95% confidence interval and values of $p < 0.05$ considered to be statistically significant. We used the paired samples t-test for comparison of weight, length and head circumference z-scores at birth, discharge/transfer and follow-up and independent samples t-test to compare the two groups. We obtained frequencies and percentage in the categorical variables and used the Chi-Square test for comparison. Linear regression (simple or multiple) was used to determine the variables that influence discharge and follow-up z-scores.

Results

A total of 262 newborns were evaluated, with a 60.3% follow-up at 2 years old (group 1 n = 158, group 2 n = 104).

The differences between the groups were statistically significant regarding comorbidities (PDA, NEC, intraperiventricular haemorrhage and infection) (see demographic data in **Tab. 1**).

In group 1 (mean GA 29 weeks), we found significant differences between weight, length and head circumference z-score at birth, discharge and follow-up. Weight and length follow-up z-scores were close to birth z-scores, although inferior, particularly at GA extremes (**Tab. 2**).

In weight z-score (**Fig. 1**) there were significant differences at all stages of evaluation (birth-discharge and discharge-follow-up, p = 0.000 and birth-follow-up, p = 0.002), as well as length z-score (birth-discharge, discharge-follow-up and birth-follow-up, p = 0.000) (**Fig. 2**).

At follow-up (**Fig. 1** and **Fig. 2**), weight and length at birth z-scores were not recovered, although some children had a higher z-score.

We also observed a significant difference in head circumference z-score (**Fig. 3**) measured at discharge and follow-up (p = 0.000) and birth and follow-up at 2 years (p = 0.003). This difference was not found when comparing birth and discharge (p = 0.189). Follow-up head circumference z-score exceeded birth head circumference z-score.

Regarding weight (**Fig. 4**), length (**Fig. 5**) and head circumference (**Fig. 6**) z-score distribution

Table 1. Demographic, comorbidities and feeding characteristics of group 1 and group 2.

	Group 1 (n = 158)	Group 2 (n = 104)	p-value
Gender	Male 82 (51.9%)	Male 47 (45.2%)	0.288078[b]
Mean GA at birth (weeks, days)	29.36899 ± 2.652265[a]	30.1375 ± 2.254884[a]	0.012566[c]
Mean birthweight z-score	-0.33539 ± 0.69821[a]	-0.49409 ± 0.781356[a]	0.095089[c]
Mean length z-score at birth	-0.5359 ± 0.928207[a]	-0.68042 ± 1.034592[a]	0.251299[c]
Mean head circumference z-score at birth	(n = 157) -0.63159 ± 0.971933[a]	-0.32282 ± 1.0077[a]	0.014765[c]
Mean weight z-score at discharge	(n = 128) -1.90563 ± 1.334214[a]	(n = 79) -1.83633 ± 0.881196[a]	0.653347[c]
Mean length z-score at discharge	(n = 127) -2.01244 ± 1.524923[a]	(n = 78) -1.76769 ± 1.216979[a]	0.206605[c]
Mean head circumference z-score at discharge	(n = 128) -0.89383 ± 1.351347[a]	(n = 79) -0.89013 ± 1.025494[a]	0.98224[c]
Mean age at discharge (days)	27.37975 ± 5.188925[a]	-	0.246309[c]
Enteral feeding	(n = 142) Human milk – 77 (54.2%) Formula – 65 (45.8%)	(n = 64) Human milk – 39 (60.9%) Formula – 25 (39.1%)	0.368742[b]
Mean time of mechanical ventilation (days)	7.56962 ± 14.70533[a]	10.60194 ± 12.52945[a]	0.076[c]
PDA	52 (32.9%)	69 (66.3%)	OR 2.297285[b] (group 2)
NEC	9 (5.7%)	21 (20.2%)	OR 1.956627[b] (group 2)
Late-onset sepsis or meningitis	75 (47.5%)	4 (3.8%)	OR 2.093[b] (group 1)
Intraventricular haemorrhage	Grade 1 – 26 (16.6%) Grade 2 – 7 (4.5%) Grade 3 – 13 (8.3%)	Grade 1 – 2 (1.9%) Grade 2 – 102 (98.1%)	-

p-value < 0.05 for statistically significant differences.
GA: gestational age; PDA: patent ductus arteriosus; NEC: necrotising enterocolitis; OR: odds ratio.
[a] Mean and standard error; [b] Chi-square test; [c] t test.

Table 2. Group 1 description.

		Minimum	Maximum	Mean	SD
GA (weeks, days)		24	34	29.37	2.652
Birth	**Weight z-score**	-2.79	1.34	-0.3354	0.69821
	Length z-score	-4.42	3.09	-0.5359	0.92821
	Head circumference z-score	-3.59	1.78	-0.631588	0.9719334
Age at discharge (days)		10.0	271	60.139	40.7615
Discharge	**Weight z-score**	-6.80	2.98	-1.9056	1.33421
	Length z-score	-7.00	2.81	-2.0124	1.52492
	Head circumference z-score	-6.67	3.21	-0.8938	1.35135
Age at exclusive enteral feeding (days)		2.00	87.0	18.3467	14.65278
Exclusive enteral feeding duration (days at the hospital)		5.00	242.0	36.14	30.750
Age at follow-up (months)		22.0	51	27.3797	5.18892
Follow-up	**Weight z-score**	-3.68	2.24	-0.6532	1.23652
	Length z-score	-4.61	2.39	-1.0712	1.31422
	Head circumference z-score	-4.66	3.66	-0.2580	1.46645

SD: standard deviation; GA: gestational age.

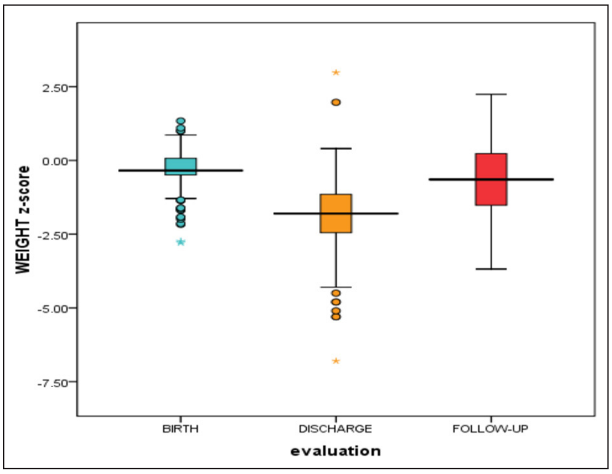

Figure 1. Boxplot of weight z-scores between birth, discharge and follow-up.
X-axis represents evaluation moments; y-axis represents z-score.

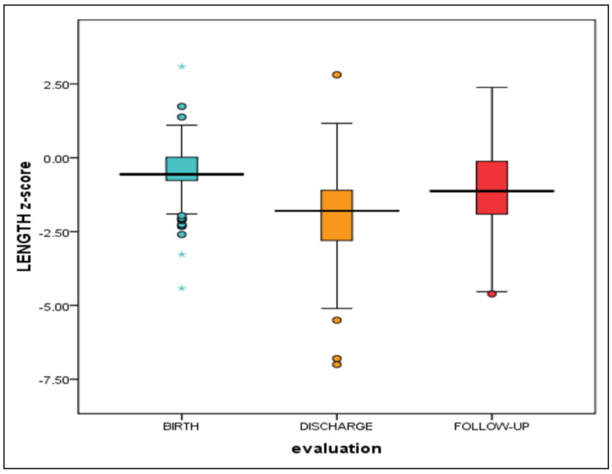

Figure 2. Boxplot of length z-scores between birth, discharge and follow-up.
X-axis represents evaluation moments; y-axis represents z-score.

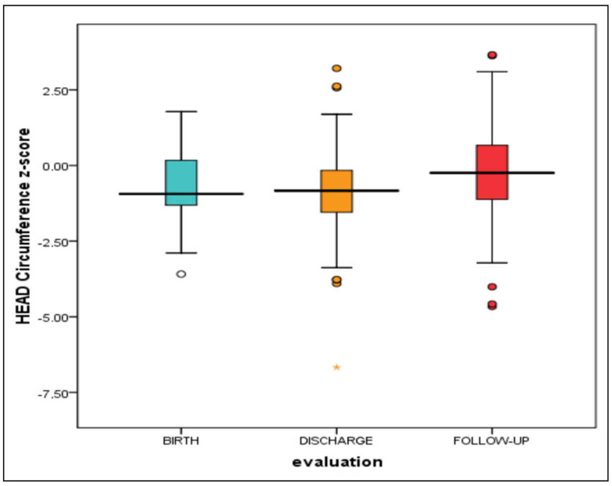

Figure 3. Boxplot of head circumference z-scores between birth, discharge and follow-up.
X-axis represents evaluation moments; y-axis represents z-score.

by the GA at birth, we found that discharge z-score is clearly inferior to other evaluation measurements.

Birth weight z-score is the only variable that positively affects weight z-score (**Tab. 3**). Follow-up weight z-score is positively affected by weight z-score at birth and negatively affected by the extent of in-hospital exclusive enteral feeding. GA and age at onset of exclusive enteral feeding do not present significant correlation.

Intraperiventricular haemorrhage is associated with lower head circumference z-score at follow-up; in contrast, larger head circumference z-score at discharge and weight z-score at follow-up are associated with larger head circumference at follow-up.

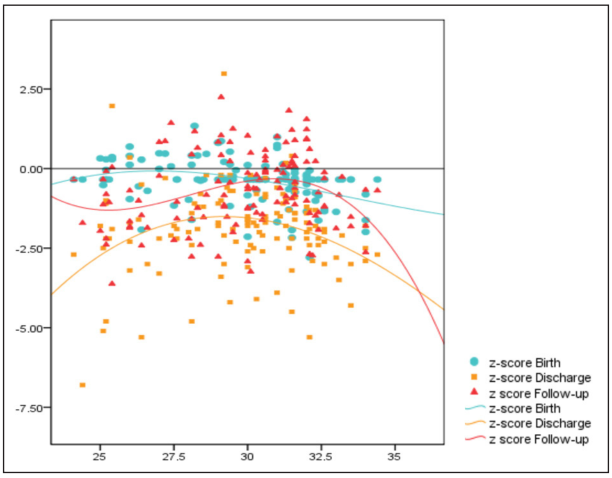

Figure 4. Fitted line plot of weight z-score at birth, discharge and follow-up according to gestational age (GA).
X-axis represents GA; y-axis represents z-score.

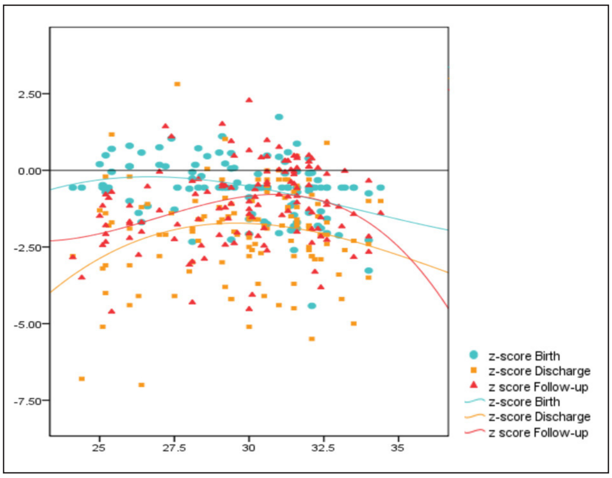

Figure 5. Fitted line plot of lenght z-score at birth, discharge and follow-up according to gestational age (GA).
X-axis represents GA; y-axis represents z-score.

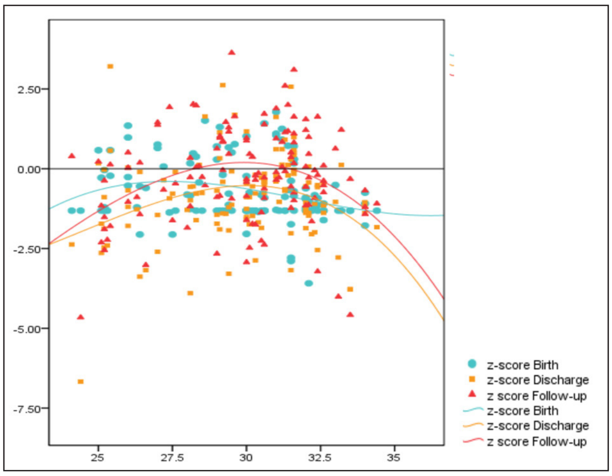

Figure 6. Fitted line plot of head circumference z-score at birth, discharge and follow-up according to gestational age (GA).
X-axis represents GA; y-axis represents z-score.

Discussion

One limitation of this study is the high number of children without follow-up (39.7%) that is higher than the 20% loss of follow-up limit considered by the AAP [12], although it is lower than the 45% loss of follow-up found in another national study (multicentre results) [13].

Another limitation (of which authors are aware) is the size of the sample, that is not representative of the country, but of one NICU. Moreover, measurements of weight, length and height were not rigorously standardized, and the timing of follow-up was not specifically planned for the study; most of the children included in group 2 that were transferred to other hospitals had follow-up in other places.

In addition, children at follow-up group (group 1) had lower GA and an increased risk of infection, so they might have had a better follow-up.

Postnatal growth patterns can be calculated using different reference data. Fenton charts were used for birth and discharge, WHO growth charts were used later. As in other studies, we chose z-scores because there were different stages and different ages of evaluation and z-scores allow us to determine the distance between the patient measurements and normal population average [14, 15] and this is one of the main strengths of our study.

Catch-up growth can be defined as a weight and length gain greater than the estimated intrauterine growth curve and is addressed to all premature infants [16]. Catch-up growth can also be defined as a z-score variation above 0.67, which corresponds to an ascension of a channel in the percentile curves [2]. On the opposite, growth failure, also termed "catch-down growth", can be defined as a decrease in weight z-score more than 0.67 [15].

The study found malnutrition on discharge and follow-up, highlighted by a lack of weight and length z-scores recovery at birth in most of the preterm infants.

Growth failure at follow-up is more evident in extreme premature infants (below 28 weeks of GA) and in preterm infants with GA above 32 weeks [1, 5, 6, 13, 15, 17-21], probably with IUGR [22].

The head circumference z-scores were higher at the 3 stages of evaluation than weight and length, as confirmed by other studies, which indicate that brain growth is not related with poor somatic growth [14, 15, 20].

Table 3. Linear regression analysis of the variables influencing weight z-score at discharge and follow-up and head circumference z-score at follow-up of group 1.

Model		Independent variables	B	Sig.
Dependent variable: weight z-score at discharge	All variables included [a]	Weight z-score at birth	0.720	0.000
		GA	-0.211	0.002
		Age at exclusive enteral feeding	-0.033	0.000
		Duration of in-hospital exclusive enteral feeding	-0.024	0.000
		Breast milk	0.421	0.046
Dependent variable: weight z-score at follow-up	All variables included [b]	Weight z-score at birth	0.6215	0.0091
	Only significant variables (all variables considered [c])	Weight z-score at birth	0.2687	0.0165
		Duration of in-hospital exclusive enteral feeding	-0.0095	0.0061
Dependent variable: head circumference z-score at follow-up	All variables included [c]	Intraperiventricular haemorrhage	-0.3738	0.0387
		Head circumference z-score at discharge	0.4309	0.0021
		Weight z-score at follow-up	0.6143	0.0001

GA: gestational age.
[a] Sex, gestational age (GA), breast milk, age at exclusive enteral feeding, in-hospital exclusive enteral feeding duration; [b] sex, GA, breast milk, late-onset sepsis/meningitis, oxygen at week 36 corrected age (CA), persistent ductus arteriosus (PDA), necrotising enterocolitis (NEC), intraperiventricular haemorrhage, age at exclusive enteral feeding, duration of in-hospital exclusive enteral feeding; [c] sex, GA, weight z-score at birth, head circumference z-score at birth, late-onset sepsis/meningitis, oxygen at week 36 CA, PDA, NEC, intraperiventricular haemorrhage, weight z-score at discharge, head circumference z-score at discharge, weight z-score at follow-up, breast milk.

Some studies describe that catch-up begins with head-circumference, continues with length and later with weight, as a biological prioritization of growth [2, 4, 20, 21, 23].

Authors remark the importance of a long-term follow-up and genetic potential based on the average height of the parents [1, 23]. Extrauterine growth restriction (EUGR) could be used as an objective measure of premature infants nutritional care quality [18, 20].

Another goal of the study is to analyze the effect of breast milk in the neonatal period. We concluded that the benefits of human milk (nutritional, gastrointestinal, immunologic and developmental) can also influence preterm infants, although breast milk composition of premature mothers does not fulfill their nutritional needs. The nutritional deficits of unfortified breast milk can be adjusted through adequate supplementation with fortifiers [8, 24]. Breast milk was associated with better weight gain at discharge and had no effect at follow-up – a new finding that contrasts with other small studies [19, 24]. The authors showed higher rates of weight gain and linear growth in formula-fed infants, but no effect on head growth [25, 26].

Lack of knowledge for the exact timing of breast milk introduction during hospitalization and the extent of exclusive or mixed breastfeeding after discharge are limitations of this study. It is known that mothers of prematures face many challenges at NICUs when starting breast milk expression and to continuing its production during hospitalization [8, 24]. It is, therefore, essential to encourage starting the process in the NICUs and keeping with it after discharge [27, 28].

Regarding growth, a first analysis may consider that nutritional strategies with formula are better than human milk (mother's milk or donor breast milk). This addresses us to the question raised by Thureen about "catch-up growth or beneficial undernutrition in VLBW" as "the Neonatologist's dilemma" [29]. There is increasing evidence showing that the growth rates of preterm adequate for GA should be different from IUGR preterm infants, because the latter were prenatally programmed to survive on low nutrient intake. So, any neonatal nutritional excess leading to rapid rates of growth until childhood predisposes to long-term health problems, increasing the risk for cardiovascular disease, hypertension, obesity, insulin resistance, impaired glucose tolerance and type 2 diabetes [2, 29, 30]. In contrast, slower growth appears to be protective against later development of cardiovascular disease [29]. At follow-up, most of the children did not regain growth, although there were also overweight children.

Further studies are needed to determine the best model to assess growth in a clinical setting.

Conclusion

This study highlights how a deficient nutritional status at discharge delays a growth recovery at 2 years of age, emphasizing the influence of birth weight and breast milk on growth. We also found evidence for the impact of prematurity itself, EUGR and neonatal morbidity on the growth of VLBW infants.

Declaration of interest

Tânia Moreira on behalf of all the Authors declares that they do not have current or potential conflict of interests that might have influenced them in the results of the present study. For the present study no funding or other financial support was required.

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