

Extrauterine growth restriction: Universal problem among premature infants

Restrição de crescimento extrauterino: problema universal entre os prematuros

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ABSTRACT

Objective

To analyze the growth rate of premature infants in the first weeks of life and factors associated with extrauterine growth restriction.

Methods

This is a cross-sectional study of 254 premature infants in a neonatal intensive care unit conducted from January 1, 2008 to December 31, 2010. Infants who died or had malformations incompatible with life were excluded. Median weight curves according to gestational age were constructed for the first four weeks of life. The Fenton growth chart calculations provided the weight Z-scores. Extrauterine growth restriction was defined as corrected weight-for-age Z-score ≤ -2 . Perinatal, morbidity, and health care variables were analyzed. The Poisson regression model yielded the prevalence *ratios*. Associations between extrauterine growth restriction and the perinatal, morbidity, and care variables were investigated. Poisson regression controlled possible confounding factors.

Results

The frequency of extrauterine growth restriction was 24.0%. Most (85.0%) small-for-gestational-age infants developed extrauterine growth restriction; 55.3% of extrauterine growth restriction cases involved small-for-gestational-age infants. Premature infants with gestational age >32 weeks did not recover the median birth weight until the third week of life and had a higher frequency of small-for-gestational-age. The Z-scores of

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Article based on doctoral dissertation of BAC FREITAS, intitled “*Restrição do crescimento extrauterino, amamentação e avaliação da adesão e influência da suplementação com micronutrientes nas prevalências de deficiências de ferro, zinco e vitamina A em prematuros*”. Universidade Federal de Viçosa; 2015.

non-small-for-gestational-age infants decreased more after birth than those of small-for-gestational-age infants. extrauterine growth restriction was associated with small-for-gestational-age (PR=6.14; 95%CI=3.33-11.33; $p<0.001$) and time without enteral diet (PR=1.08; 95%CI=1.04-1.13; $p=0.010$).

Conclusion

Extrauterine growth restriction occurs in premature infants of all gestational age. The participation of small-for-gestational-age and nutritional practices in its genesis is noteworthy. We suggest prospective studies of all premature infants. The implementation of best care practices, individualized for small-for-gestational-age infants, to improve nutrient supply can minimize the problem.

Keywords: Growth and development. Infant, premature. Malnutrition.

RESUMO

Objetivo

Analisar o crescimento de prematuros nas primeiras semanas de vida e fatores associados à restrição de crescimento extrauterino.

Métodos

Estudo transversal realizado entre 01/01/2008 e 31/12/2010 com 254 prematuros em unidade de terapia intensiva. Excluíram-se óbitos e malformações incompatíveis com a vida. Construíram-se curvas de medianas de peso para as quatro primeiras semanas de vida de acordo com a idade gestacional. Calcularam-se escores-Z do peso pela planilha Fenton growth chart calculations. Definiu-se restrição de crescimento extrauterino pelos escores-Z do peso ≤ -2 para a idade corrigida na alta hospitalar. Analisaram-se associações entre variáveis perinatais, assistenciais e morbidades com a restrição de crescimento extrauterino. Utilizou-se a regressão de Poisson para controlar os possíveis fatores de confundimento.

Resultados

A frequência de restrição de crescimento extrauterino foi de 24%. Dos pequenos para a idade gestacional, 85% evoluíram com restrição de crescimento extrauterino. Prematuros com idade gestacional >32 semanas não recuperaram medianas de peso ao nascer até a terceira semana de vida, e, dentre eles, estava a maior frequência de pequenos para a idade gestacional. Os não pequenos para a idade gestacional apresentaram maior queda do escore-Z de peso do nascimento à alta quando comparados aos pequenos para a idade gestacional. Associaram-se à restrição de crescimento extrauterino nascer pequeno para a idade gestacional (RP=6,14; IC95%=3,33-11,33; $p<0,001$) e tempo sem dieta enteral (RP=1,08; IC95%=1,04-1,13; $p=0,010$).

Conclusão

A restrição de crescimento extrauterino ocorre entre prematuros de todas as idades gestacionais, ressaltando-se a participação do nascimento pequeno para a idade gestacional e das práticas nutricionais na sua gênese. Sugerem-se estudos prospectivos que envolvam todos os prematuros. A implementação de boas práticas assistenciais que visem melhorar a oferta nutricional e individualizada para os pequenos para a idade gestacional pode minimizar o problema.

Palavras-chave: Crescimento e desenvolvimento. Prematuro. Desnutrição.

INTRODUCTION

Extrauterine Growth Restriction (EUGR) in premature infants is an object of studies and results from a complex interaction between genetic and environmental factors, which affect nutritional requirements, endocrine disorders, and treatments^{1,2}.

Growth involves genetic potentials that may or may not be reached, depending on the

individual's life conditions from conception until adulthood. Prematurity is a determinant for stunting, with repercussions on adulthood^{3,4}. Premature infants who are small for gestational age or with EUGR at hospital discharge are at greater risk of stunting and its long-term consequences^{1,2}.

Morbidities that affect premature infants, such as hyaline membrane disease, prolonged ventilatory support, neonatal sepsis, bronchopul-

monary dysplasia, and anemia, impact their postnatal growth^{3,5,6}.

Extrauterine growth restriction is a marker of severe nutritional deficit during the first weeks of life, which can be assessed at 36 weeks of corrected age or at discharge based on reference intrauterine or postnatal growth curves^{3,7,8}. Fenton & Kim⁹ curves, which became available recently, are considered the standard postnatal growth curves⁹⁻¹¹. As gestational age and birth weight decrease, weight regain becomes harder, consequently increasing the incidence of EUGR. To decrease the incidence of EUGR and its consequences, protocols that improve the nutrient supply for premature infants, especially infants at higher risk, must be implemented and updated^{12,13}.

The survival of increasingly premature infants has resulted in many studies with Very-Low-Birth-Weight (VLBW) infants. However, there is a scarcity of studies with premature infants with a gestational age of 32 weeks or more, especially because 70% of premature infants have a gestational age of 34 weeks or more¹⁴.

In face of the above, the following questions arise: what is the growth rate of premature infants during the first weeks of hospital stay? How do gestational age, birth weight, and morbidities affect growth rate? What factors are associated with EUGR? Are there modifiable factors?

In order to answer these questions, this study assessed the growth rate of premature infants during the first weeks of extrauterine life and investigated the factors associated with extrauterine growth restriction at discharge from a Neonatal Intensive Care Unit (NICU).

METHODS

This cross-sectional, retrospective study used secondary data from the medical records of premature infants admitted to the NICU of the *Hospital São Sebastião* in Viçosa (MG) from January 1, 2008 to December 31, 2010.

The sample size was calculated by Stat Calc of Epi Info 7.0 (Centers for Disease Control and Prevention, Atlanta, Georgia, United States). A total of 140 premature infants would be needed for an EUGR prevalence of 26%¹⁵, a power of 90%, and a significance of 95%.

The study included live premature infants with birth weight >500 g and medical records with data from birth until discharge. Infants who died or had malformations incompatible with life were excluded. As a result, 254 premature infants were included.

Gestational age was obtained from the medical record and defined as the best estimate between early gestational ultrasound (<20 weeks), date of the last period, obstetric notes, and clinical examination using the New Ballard Score^{16,17}. The corrected age was given by adding each week of postnatal life to the gestational age at birth^{3,18}.

The medical records included the weights of the premature infants in the first four weeks of life (birth weight and on days 6, 13, and 27) and at discharge. The median weight (50th percentile) for gestational age at birth and median corrected age at discharge were calculated, considering the number of completed weeks. Hence, curves of the median birth weight and weight at 6, 13, and 27 days of life were constructed.

Extrauterine growth restriction was defined as a weight-for-corrected age Z-score ≤ -2 at discharge¹⁹, also considered the outcome variable. The weight Z-scores were calculated using the spreadsheet Fenton Growth Chart Calculations^{9,20}.

Birth weight and gestational age adequacy were given by the Fenton & Kim⁹ curves, and the infants were classified according to birth weight Z-score. The infants were classified as appropriate for gestational age when birth weight Z-score > -1.29 (10%) and small for gestational age when birth

weight Z-score ≤ -1.29 (10%). The infants were also classified as appropriate for gestational age when they were between the tenth and ninetieth percentiles and large for gestational age when they were above the ninetieth percentile^{9,20}.

Fenton & Kim⁹ curves were used because they were based on a meta-analysis with the highest number of newborns to date and their respective data; the authors used the data to construct new curves for newborn growth assessment according to gestational age. According to the Portuguese Society of Pediatrics¹¹, these curves approach a new standard curve. In addition to assessing fetal growth at birth, they allow monitoring the postnatal growth of premature infants until they reach a corrected age of 50 weeks as the data were harmonized with the World Health Organization²¹ curve from the 40th week onward^{9,11}.

Qualitative explanatory variables: gestational age was categorized according to the number of completed weeks: <28 weeks (extremely premature); between 28 and 31 weeks (very premature); and between 32 and 36 weeks (moderately premature)¹⁶; sex was categorized as female or male; and the small for gestational age variables bronchopulmonary dysplasia²², late-onset neonatal sepsis (occurring after the first 48 hours of life)²³, and transfusion of red blood cell concentrates were categorized in a binary fashion (yes/no).

Quantitative explanatory variables: gestational age (weeks and days); corrected age at discharge (weeks and days); birth weight and weight at discharge (grams); birth weight and weight at discharge Z-scores; length of hospital stay (days); duration of mechanical ventilation (days); total days of supplemental oxygen (days); age at start of enteral diet (days); age at start of parenteral nutrition (days); age at start of adequate enteral intake (days; considered as 150 mL/kg/day)^{24,25}; and days without enteral diet.

The study population was characterized by frequencies and measures of central tendency and dispersion. The Kolmogorov-Smirnov test

showed that only the variables weight and weight Z-scores had normal distribution, so they were expressed as means and standard deviations. The other quantifiable variables were expressed as medians, 25th percentile, and 75th percentile. The qualitative variables were compared by the Pearson's Chi-square test or Fisher's exact test, and the quantitative variables by the Mann-Whitney, Kruskal-Wallis, or Student's *t* tests.

Bivariate analyses were performed between the explanatory and outcome variables, obtaining, as a measure of effect, Prevalence Ratios (PR) using Poisson regression²⁶. Variables with $p < 0.20$ were included in multivariate analysis, and variables with $p < 0.05$ were maintained in the final model.

The weight curves were constructed by adjusting a third-degree polynomial function to smooth the curves and thereby suppress small variations in their curvatures.

The programs Excel (Microsoft Office, Redmond, Washington, United States) version 2010, Stata (Stata Corporation, College Station, Texas, United States) version 9.1, and Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, United States) version 20.0, for Windows were used for creating the database, and codifying, entering, and statistically analyzing the data.

The study was approved by the Research Ethics Committee of the *Universidade Federal de Viçosa*, under Protocol nº 063/2011, and did not require Signed Informed Consent. The study ensured the secrecy and confidentiality of all study participants' data.

RESULTS

A total of 293 premature infants were eligible during the study period. However, 13.3% of the premature infants ($n=39$) died and were excluded from the study, resulting in a population of 254 premature infants. Table 1 characterizes the study population, which had an EUGR prevalence of 24.0%.

Table 1. Birth, hospital stay, and hospital discharge characteristics of premature infants. Viçosa (MG), Brazil, 2008-2010 (n=254).

Variables	Birth					
	n	%	Mean	SD	Median	P ₂₅ -P ₇₅
Sex						
Male	145	57.1				
Female	109	42.9				
Gestational age (weeks)						
<28	21	8.3				
28-31	75	29.5				
32-36	158	62.2				
Birth weight/gestational age*						
Appropriate for gestational age	203	79.9				
Small for gestational age	40	15.7				
Large for gestational age	11	4.3				
Gestational age			--	--	33.0	30.6 - 34.3
Weight			1,818.1	648.6	--	--
Weight Z-score			-0.335	0.952	--	--
Hospital stay						
Late-onset sepsis	61	24.0				
Bronchopulmonary dysplasia	27	11.3				
Transfusion of red blood cell concentrate	84	33.1				
Days of mechanical ventilation					4.0	2.0 - 14.0
Days of oxygen					4.5	1.0 - 17.0
Days at start of enteral diet					2.0	1.0 - 4.0
Days at start of parenteral nutrition					3.0	2.0 - 4.0
Days at start of adequate enteral intake					15.0	9.0 - 22.5
Days without enteral diet					3.0	1.0 - 5.0
Discharge						
EUGR						
Yes	61	24.0				
No	193	76.0				
Corrected age			--	--	36.0	35.1 - 37.3
Weight			2,209.3	479.1	--	--
Weight Z-score			-1.332	-1.132	--	--
Days of hospital stay			--	--	18.0	9.0 - 40.0

Note: *Classification based on the Fenton & Kim^{9,10} curves. Results expressed as number (%). The percentage of the categories refers to the total number of valid answers. Missing data were not considered.

SD: Standard Deviation.

Since the first weeks of life are an important time for growth, curves of the median weight of the premature infants were constructed according to their gestational age at birth for the first four weeks of life (Figure 1).

The median birth weight tended to increase as gestational age increased. At six days of life, weight had decreased. At thirteen days, premature infants with gestational age <33 weeks had regained their weight. However, a critical point appeared for premature infants with

gestational age >33: they had had no weight regain by the thirteenth or the twentieth day. At 27 days of life, premature babies with gestational age at birth >33 weeks had not yet regained their weight.

Bivariate analyses of the premature infants' characteristics from birth until NICU discharge were conducted, establishing EUGR as outcome (Table 2). The significant ($p < 0.05$) variables were: female sex, small for gestational age, late-onset sepsis, smaller measurements at birth and

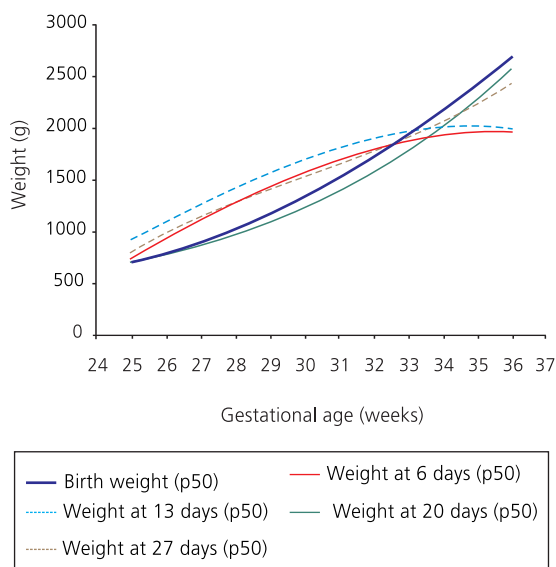


Figure 1. Median weight change per week on premature infants' first 27 days after birth according to gestational age at birth. Viçosa (MG), Brazil, 2008-2010

discharge, longer hospital stay, higher age at start of adequate enteral intake, and longer time without enteral diet.

These variables were submitted to bivariate Poisson regression for the outcome EUGR. The variables that persisted with $p < 0.20$ were included in multivariate analysis: small for gestational age, sex, birth weight, neonatal sepsis, red blood cell concentrates, age at start of enteral diet, age at start of adequate enteral intake, and days without enteral diet. The variable gestational age was a confounding factor.

In the final regression model, the following variables remained associated with EUGR: small for gestational age at birth (PR=6.14; 95%CI=3.33-11.33; $p < 0.001$) and days without enteral diet (PR=1.08; 95%CI=1.04-1.13; $p = 0.010$) Table 3.

The variables small for gestational age at birth and days without enteral diet were analyzed by gestational age strata in an attempt to explain the behavior of the weight curves in Figure 1. Small for gestational age did not occur in premature infants with gestational age < 28 weeks. Small for gestational age frequency was

higher in the ≤ 32 gestational age ≤ 36 weeks' strata ($p = 0.001$). This occurred because the number of deaths increased as gestational age decreased ($p < 0.0001$), and all small for gestational age < 28 weeks died (data not shown). The variable days without enteral diet also differed by gestational age stratum ($p < 0.0001$): time without diet decreased as gestational age increased (Table 3).

Most (85.0%) of the infants born small for gestational age had EUGR at discharge, and 55.3% of the infants with EUGR were small for gestational age at birth. However, 44.3% of the EUGR were not small for gestational age. In a time line, 15.7% of the population was small for gestational age at birth, but 24.0% had EUGR at discharge.

Figure 2 shows how the mean weight Z-scores changed from birth to discharge in small for gestational age and non- small for gestational age infants. Small for gestational age infants had a mean weight Z-score of $-1.81 (\pm 0.39)$ at birth and $-2.74 (\pm 0.78)$ at discharge. Non- small for gestational age infants had a mean weight Z-score of $-0.06 (\pm 0.75)$ at birth and $-1.07 (\pm 0.98)$ at discharge.

The differences between the weight Z-scores at birth and discharge measured by the Student's t test were significant for small for gestational age and non- small for gestational age infants ($p < 0.0001$): the small for gestational age infants had a smaller weight Z-score loss (difference of 0.93), while non- small for gestational age had higher weight loss (difference of 1.01).

DISCUSSION

Extrauterine grown restriction between birth and a corrected age of 40 weeks is a proven risk factor for stunting and neurodevelopment deficit in the first two years of life^{3,27}. Therefore, it is important to unveil the factors involved in EUGR genesis and intervene accordingly.

Table 2. Characteristics of premature infants according to extrauterine growth restriction. Viçosa (MG), Brazil, 2008-2010 (n=254).

Variables	Extrauterine growth restriction				p-value
	Yes		No		
	n=61	%	n=193	%	
Sex					0,009*
Male	26	17.9	119	82.1	
Female	35	32.1	74	67.9	
Small for gestational at birth					<0.0001*
Yes	34	85.0	6	15.0	
No	27	12.6	187	87.4	
Late-onset sepsis					0.004*
Yes	23	37.7	38	62.3	
No	38	19.7	155	80.3	
Bronchopulmonary dysplasia					0.269*
Yes	9	33.3	18	66.7	
No	50	23.6	162	76.4	
Red blood cell concentrate					0.069*
Yes	26	31.0	58	69.0	
No	35	20.6	135	79.4	

Variables	Extrauterine growth restriction								p-value
	Yes				No				
	Mean	SD	Median	P ₂₅ -P ₇₅	Mean	SD	Median	P ₂₅ -P ₇₅	
Gestational age (weeks, days)	--		33.1	31.4-34.4	--		33.0	30.1-34.3	0.142**
Birth weight (g)	1,498.70	366.90	--	--	1,919.10	685.30	--	--	<0.0001***
Birth weight Z-score	-1.38	0.71	--	--	-0.01	0.61	--	--	<0.0001***
Hospital stay (days)	--	--	27.0	13.0-46.5	--	--	14.0	8.0-35.5	<0.004**
Days of mechanical ventilation	--	--	7.0	1.0-14.0	--	--	4.0	1.0-14.0	0.121**
Days of oxygen therapy	--	--	4.0	1.5-25.0	--	--	4.5	1.0-15.8	0.805**
Days at start of enteral diet	--	--	3.0	1.3-5.0	--	--	2.0	1.0-3.0	0.003**
Days at start of parenteral nutrition	--	--	3.0	2.0-5.0	--	--	3.0	2.0-4.0	0.204**
Days at start of adequate enteral intake	--	--	19.0	11.3-29.8	--	--	14.0	7.0-21.0	0.001**
Days without enteral diet	--	--	4.0	2.0-8.5	--	--	2.0	1.0-4.0	<0.0001**
CA at discharge (weeks, days)	--	--	37.2	36.0-39.0	--	--	35.5	34.6-37.0	<0.0001**
Weight at discharge (g)	1,886.90	266.30	--	--	2,312.20	486.70	--	--	<0.0001**
Weight Z-score at discharge	-2.84	0.89	--	--	-0.85	0.69	--	--	<0.0001***

Note: *p-value according to Pearson's Chi-square test; **p-value according to Mann-Whitney test; ***p-value according to the Student's t test. Results expressed as number (%). The percentage of the categories refers to the total number of valid answers. Missing data was not considered. Significance level: p<0.05. SD: Standard Deviation; CA: Corrected Age.

Extrauterine grown restriction prevalence in the sample was 24.0%, and being small for gestational age at birth increased the likelihood of EUGR by 6.14 times, while each day without enteral diet increased its likelihood by 8.0%. In a Brazilian study, de Lima *et al.*¹⁵ found that EUGR affects 26.0% of premature infants, and small for gestational age at birth has more impact than

any other variable. Gianini *et al.*²⁸ also associated small for gestational age at birth with EUGR. Other studies have also found this association, but the EUGR rates varied from 16.0 to 63.0%²⁹⁻³². Shan *et al.*³² found EUGR in 44.0% to 62.2% of premature infants.

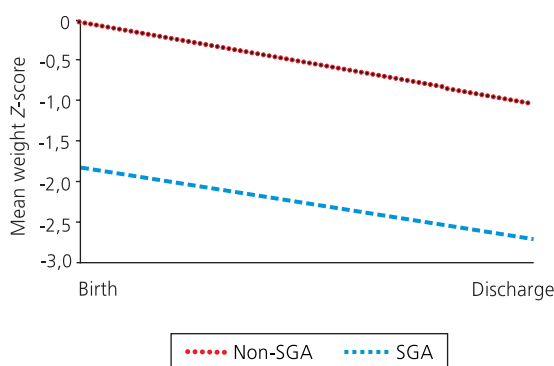
In this study 85% of the small for gestational age -at-birth infants had EUGR at

Table 3. Variables in the final multivariate Poisson regression model for the outcome extrauterine growth restriction and their distributions according to gestational age strata. Viçosa (MG), Brazil, 2008-2010.

Variables	PR		95%CI		p-value		
SGA at birth	6.14		3.33 - 11.33		<0.001		
Days without enteral diet	1.08		1.04 - 1.13		<0.010		
	GA <28 weeks ^a		GA 28-31 weeks ^b		GA 32-36 weeks ^c		
	n	%	n	%	n	%	
SGA at birth							0.001*
Yes	--	--	4	10.0	36	90.0	
No	21	9.8	71	33.2	122	57.0	
	Median	P ₂₅ -P ₇₅	Median	P ₂₅ -P ₇₅	Median	P ₂₅ -P ₇₅	
Days without enteral diet	5.5	3.3-10.0	3.0	2.0-6.0	2.0	1.0-4.0	<0.0001*

Note: *p-value according to Fisher's exact test, testing b and c (it was not possible to test a for association because of its zero frequency); **p-value according to the Kruskal-Wallis test. The model included the following variables with $p < 0.20$ in bivariate analysis: Small for Gestational Age (SGA) at birth, sex, neonatal sepsis, red blood cell concentrate, age at start of enteral diet, age at start of adequate enteral intake, and days without enteral diet; the variable gestational age was a confounding factor. Results expressed as number (%). The percentage of categories refers to the total number of valid answers. Missing data were not considered. Significance level: $p < 0.05$.

PR: Prevalence Ratio; 95%CI: 95% Confidence Interval; GA: Gestational Age.

**Figure 2.** Weight Z-scores during the hospital stay. Viçosa (MG), Brazil, 2008-2010.

Note: Small for Gestational Age (SGA) infants lost less weight Z-score (difference of 0.93) while non-SGA infants lost more weight (difference of 1.01) - Student's *t* test; $p < 0.001$.

discharge. Data from the Neonatal Surveys Network of the National Institute of Child and Human Development (NICHD) found that 16% of premature infants were small for gestational age at birth, and 89% of these infants continued small at corrected age 36 weeks, corroborating the association between EUGR and small for gestational age at birth^{31,33}.

In a previous study with this population, Freitas *et al.*³⁴ found a frequency of small for gestational age at birth of 11.3% using as

reference Lubchenco's *et al.*³⁵ curves, confirming the association between small for gestational age at birth and higher odds of death, which was corroborated by Larroque *et al.*³⁶ However, if the data were revisited and the Fenton & Kim⁹ curves were used, this prevalence would increase to 17.7%, which is important when considering the associations between small for gestational age at birth and the outcomes EUGR and death.

The variation in EUGR prevalence can be explained by sample differences, use of different reference curves, and use of different cut-offs to characterize the outcome. Although the American Academy of Pediatrics recommends that extrauterine growth rate should aim to equal intrauterine growth rate of a premature infant with same gestational age^{2,29}, the postnatal growth curves seem more appropriate to follow their growth³⁷, and currently, the Fenton & Kim⁹ and Fenton *et al.*¹⁰ curves approach the standard for classifying and following newborns until the corrected age of 50 weeks¹¹. Lima *et al.*¹⁵ also disagree with the American Academy of Pediatrics recommendations.

Extrauterine grown restriction was significantly associated with longer time without enteral diet. The median ages at start of parenteral and enteral nutrition were higher than the recommended values - early use of parenteral

nutrition in the first hours of life and minimum enteral diet on the first or second day³⁸. However, adherence to the clinical protocols remains far from the ideal even in developed countries^{38,39}. Despite the absence of association in the present study, nutritional practices influence the growth rate of premature infants^{7,40,41}, and recommendations should be followed because they are widely supported by scientific evidence.

The study morbidities did not affect premature infant growth, disagreeing with Gianini *et al.*²⁸. Other researchers have found that morbidities and care practices during hospital stay, including nutritional practices, influenced newborn growth rate^{21,22,38,40,41}, and emphasized the importance of providing adequate amounts of energy and proteins^{13,42}.

Growth rate and dynamics during hospital stay are under study. It is fact that the first two weeks of life represent a critical occasion in premature infant growth^{13,42} and that inadequate growth during the first weeks after birth can be a marker of EUGR³.

The weight curves showed that the median weight of infants with gestational age <32 weeks tended to recover by 13 days of life. Moreover, moderately premature infants (gestational age at birth between 32 and 36 weeks) tended not to recover the median birth weight until the twentieth or twenty-seventh postnatal day. According to the literature, premature infants need 8 to 24 days to recover their birth weight^{28,43}. Initial weight loss, which usually occurs between the fourth and ninth postnatal day, especially on the first five days, is followed by an early growth peak, with growth rates that tend to mimic intrauterine rates from the second week onward^{33,43,44}.

The results may have been influenced by the absence of small for gestational age in infants with gestational age <28 weeks due to higher mortality as gestational age decreased. Although gestational age did not remain in the final model, it was associated with EUGR in bivariate analysis, that is, as gestational age increased, the frequency

of EUGR also increased, which may in part explain the behavior of the study curves.

There is evidence that the incidence of EUGR increases as gestational age and birth weight decrease, given that smaller premature infants lose more weight and take longer to regain the weight, and that as gestational age decreases, nutritional requirements increase and achievement of satisfactory growth rates becomes less likely. In other words, the chance of reaching a normal weight decreases as the time to achieve a normal growth rate increases^{2,41,42,45-47}. On the other hand, Shan *et al.*³² associated EUGR with an increase in gestational age, which agrees with our results.

The smaller weight Z-score loss among small for gestational age infants allows one to understand the occurrence of EUGR in non-small for gestational age infants and to elucidate the impact of longer periods without enteral diet on EUGR genesis. Lima *et al.*¹⁵ also found similar results for weight Z-scores. Embleton *et al.*⁴⁸ reinforce the multiplicity of factors involved in the development of EUGR and associate the accumulation of nutritional deficits in the first weeks after birth to nutritional practices, resulting in EUGR.

On the other hand, Ornelas *et al.*⁴⁹ found that the extrauterine growth rates of premature small for gestational age and appropriate for gestational age infants differ and that small for gestational age infants have less inclined growth curves than appropriate for gestational age until the fortieth week. Ehrenkranz *et al.*⁵⁰ reported that appropriate for gestational age infants and infants who did not develop severe morbidities had higher growth rates.

Cooke *et al.*² and Cooke⁵¹ affirms that extrauterine growth is influenced by a complex interaction of factors, that it is difficult to establish proper nutrition in ill and clinically unstable premature infants, and that when the energy and protein supplies are based on birth weight, the infants receive less food than they should.

In summary, the study showed that: 24.0% of the study premature infants developed EUGR;

small for gestational age and more time without enteral diet were associated with higher odds of developing EUGR; EUGR affected 85.0% of small for gestational age infants; 15.7% of the study sample was born small for gestational age and 24.0% developed EUGR; 55.3 and 44.3% of EUGR cases involved infants who were and were not small for gestational age at birth, respectively; moderately premature infants tended not to regain their median birth weight by the third postnatal week, and this stratum contained a higher concentration of small for gestational age infants; and non- small for gestational age infants lost more weight Z-score between birth and discharge than small for gestational age infants, reinforcing the role of nutritional practices.

The present study emphasizes the need of more studies of moderately premature infants, which include most infants born before the thirty-seventh week of gestation. The limitations include the retrospective characteristic of the study, which entails information bias (medical records) and the lack of further nutritional details.

CONCLUSION

Extrauterine growth restriction is a problem in premature infants, which is associated with small for gestational age at birth and longer periods without enteral diet. However, EUGR genesis is multifactorial, and the factors involved remain unknown. Based on the study results, we suggest more prospective studies with premature infants of all gestational ages and point out that the dissemination of information and implementation of good care practices to improve nutrient supply, individualized for small for gestational age infants, can minimize the problem.

CONTRIBUTORS

BAC FREITAS conducted the analyses and wrote the article. SE PRIORE, LM LIMA, and SCC FRANCESCHINI supervised the analyses and reviewed the article.

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Received: November 13, 2014
Final version: August 17, 2015
Approved: September 4, 2015