Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 10/17/2020
Approved on: 12/19/2020

ORIGINAL ARTICLE

Incidence of extrauterine growth restriction and associated risk and protective factors for very low birth weight newborns

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Keywords:
Growth,
Premature Newborn,
Very Low Birth Weight Infant.

Abstract

Objective: To determine the incidence of extrauterine growth restriction (RCEU) in very low birth weight (VLBW) newborn and associated factors. **Methods:** Longitudinal, prospective study with very low birth weight premature newborns in a maternity school, carried out between October/2017 to September/2018. Demographic, clinical and nutritional variables were evaluated. The curves used at birth and to monitor growth were those of the INTERGROWTH Project. RCEU was defined as a Z score of birth weight < -2. In inferential statistical analysis, chi-square, Students t, Mann-Whitney and logistic regression tests were used. **Results:** 97 children were analyzed, of which 41.2% developed RCEU. Weight, Z score at birth and caloric intake in the first week of life were higher in children without growth restriction. The use of mechanical ventilation, length of stay in intensive care unit, bronchopulmonary dysplasia and late sepsis were associated with RCEU in the bivariate analysis. In multivariate logistic regression, only the Z score of birth weight ($p<0.001$) and the use of mechanical ventilation ($p=0.006$) remained associated with the outcome. Regarding the nutritional status at birth, the higher the Z score of weight, the lower the incidence of RCEU. **Conclusion:** The incidence of RCEU found was high, with the nutritional status at birth and the use of mechanical ventilation as the main associated factors.

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DOI: 10.25060/residpediatr-2022.v12n3-490

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INTRODUCTION

Each day, the number of preterm newborns admitted to Neonatal Intensive Care Units (NICU) with increasingly lower gestational ages and birth weight grows[1,2]. This situation causes health professionals working in this segment to be more concerned about the quality of the care provided to decrease the occurrence of comorbid conditions along with proper growth and development[3,4].

Promoting proper growth and development of preterm infants has become increasingly challenging, since prematurity interrupts the supply of nutrients, especially energy and protein, during a period in which growth is accelerated, thereby placing newborns at great nutritional risk[5]. In addition, specific morbidities of prematurity cause great metabolic stress in these infants by increasing their metabolism and nutritional needs[4,6].

Inadequate nutrition in this critical period results in extrauterine growth restriction (EUGR), defined as the presence of growth deficit when weight and/or length are below the tenth percentile or when the z-score is < -2 between 36 and 40 weeks of corrected gestational age or at the time of discharge[4,7]. The occurrence of EUGR affects long-term neurocognitive development and may permanently compromise this child's life into adulthood[4,8].

Early and optimal nutritional practices, monitoring and assessment of the growth and development of these children have reduced the incidence of EUGR[9]. It is extremely important to find which nutritional and clinical factors are associated with the incidence of EUGR. This information will contribute to the improvement of care practices in institutions caring for very low birth weight (VLBW) newborns. Therefore, this study aims to determine the incidence of extrauterine growth restriction in very low birth weight preterm newborns and which factors are associated with this outcome.

METHODOLOGY

This is prospective, longitudinal cohort study was carried out at a maternity school hospital located in the care complex of the Federal University of Rio Grande do Norte, a referral center for high-risk pregnancies in the state of Rio Grande do Norte.

The study included all preterm newborns weighing < 1500 grams admitted to the NICU in the period from October 2017 to September 2018, using a convenience sample. The following exclusion criteria were applied: children with severe congenital malformations, chromosomopathies, innate error of metabolism, multiple pregnancies (> 2 fetuses), newborns transferred to other neonatal units, and infants who died during the study period.

The following variables were considered: maternal age, number of prenatal visits, sex, and 5-minute Apgar score. Gestational age was estimated based on the first trimester ultrasound or date of the last menstrual period (LMP), preferably, or if they were not available, gestational age was calculated based on the New Ballard method. Weight and length were measured by the care team, using a standardized technique, in a UBB 15/5 pediatric scale with 5-gram divisions and an anthropometric ruler with classification according to gestational age and sex through the birth charts of the Intergrowth Project.[10] Birth weight was deemed appropriate for gestational age (AGA) when it was between the 10th and 90th percentile and small for gestational age (SGA) when it was below the 10th percentile. Other independent variables were: time to regain birth weight, length of hospital and NICU stay, antenatal and postnatal corticosteroid use.

We also verified the presence of the following comorbid conditions: peri-intraventricular hemorrhage graded according to Papile,[11] necrotizing enterocolitis, and bronchopulmonary dysplasia (BPD) defined by Bell's criteria[12] and by oxygen dependence for ≥ 28 days of life,[13] respectively. Metabolic bone disease was defined based on alkaline phosphatase > 800 U/L and/or phosphorus < 5.5 mg/dl, according to the institution's protocol (assessed from 30 days after birth). Infections were considered according to the criteria defined by the ANVISA in 2017.[14]

The following feeding practices were recorded: days of parenteral nutrition and to achieve full enteral nutrition (≥ 120 ml/kg/d), predominant enteral diet (raw breastmilk, pasteurized breastmilk, and formula) and energy-protein intake in kcal/kg/d and g/kg/d, respectively, in the first week after birth and in the period from 7-27 days after birth. The nutritional support in effect at the institution is based on the use of preferably the mother's own breastmilk. In its absence, pasteurized breastmilk from the milk bank is used and, as a last resort, infant formulas are used. The nutritional practices employed in the institution are: early (in the first two days after birth) and optimized parenteral nutrition (start with 2 g/kg/day of protein up to a maximum of 3.5 g/kg/day, glucose infusion rate of 4-6 mg/kg/min moving up to 10-12 mg/kg/min, and lipid supply of 1.5 g/kg/day up to a maximum of 3 g/kg/day), early enteral nutrition (start of minimal enteral nutrition in the first two days after birth, preferably in the first 24 hours, with a volume of 10-20 ml/kg/day every 3 hours with volumes increasing at a rate of 20-35 ml/kg/day, after hemodynamic stabilization and absence of signs of food intolerance until full enteral nutrition has been achieved - 120 ml/kg/day), and use of breastmilk additives (in enteral nutrition with volumes ≥ 100 ml/Kg/day).

The calculation of the calorie and protein intake was performed daily according to the type and volume of the diet prescribed and administered. When mother's own breastmilk was administered, the amount of calories and protein present in each 100 ml was considered according to postnatal age: 1st week (60 kcal and 2.2g/protein), 2nd week (71kcal and 1.5g/protein), 3rd and 4th weeks (77kcal and 1.4g/protein), 5th week (63 kcal/1.1g/protein)[15]. In the administration of pasteurized milk from the bank milk, we considered 60kcal and 1.3g/

protein in 100 ml of milk[16]. When breast milk additive was used, the intake was the sum of the nutritional intake of raw or pasteurized breastmilk and the additive, according to the nutritional information on the label. When infant formulas were administered, the composition found on the label was used to calculate nutritional intake. The following data were recorded at discharge: corrected gestational age, weight, and length, with growth parameters categorized based on the charts for preterm infants of the Intergrowth Project[17].EUGR (at the time of discharge) was considered for weight z-score <-2[7,10].

Statistical analysis was performed using software package SPSS Statistics 22, with descriptive data evaluation (absolute and relative percentages for categorical variables and measures of central tendency and dispersion – standard deviation – for quantitative variables) and inferential analysis to find associations between variables. Categorical variables were analyzed using the chi-squared test. Student's t-test was used to compare quantitative variables between groups with and without EUGR for independent samples and the Mann-Whitney test for variables with and without normal distribution. A binary logistic regression model was built for multivariate analysis, including variables with a p-value < 0.05 in bivariate evaluation. Significance was attributed when p < 0.05 with a 95% confidence interval.

The guardians of the children included in the study signed an informed consent term. The Research Ethics Committee of Federal University of Rio Grande do Norte approved the study and issued certificate no. 76397417.5.0000.5292.

RESULTS

A total of 147 preterm infants with birth weight < 1500 grams were admitted to the NICU in the period from October 2017 to September 2018. A total of 97 infants were considered eligible. Two children were excluded due to the presence of severe congenital malformations, three for refusal from their guardians to sign the informed consent term, four for being quadruplets (unusual event, in which the birth order and multiple twins might interfere with the neonatal outcomes and endpoints studied), 38 died, and three were transferred to other units.

The characteristics of the study population are described in Table 1. More than half (52.6%) of the infants were males; mean gestational age and birth weight were 29.8 ± 2.18 weeks and 1185.5 ± 214.1 grams, respectively. As for the nutritional status at birth, 22.7% of the patients were small for gestational age and 12.4% had a weight z-score < -2. At discharge, 41.2% of the infants were diagnosed with extrauterine growth restriction. The preterm infants included in the study were discharged with a median corrected gestational age of 37.2 weeks and a weight of 1997.5 g.

The patients with EUGR had lower birth weight, fell further down the growth charts until discharge (evidenced by the z-score), stayed for more days on mechanical ventilation, had longer hospital and NICU stays, and had lower levels of calorie intake in the first week after birth. They also had more comorbid conditions such as bronchopulmonary dysplasia and late sepsis. The results are shown in Tables 2 and 3.

Table 1. Perinatal and neonatal characteristics of 97 very low birth weight newborns in Natal/RN, from October 17 to September 2018.

Variables	
Maternal Age	
<20 years	29 (29.9%)
20-34 years	54 (55.7%)
≥35 years	14 (14.4%)
No. of prenatal visits, mean (± SD)	4,7 (±2.26)
Gestational age, weeks	
Birth, mean (± dp)	29.8 (±2.18)
Discharge, median	2.18
Weight, grams	
Birth, mean (± dp)	1185.5 (±214.1)
Discharge, median	1997.5
Weight category relative to gestational age	
SGA, n (%)	22 (22.7%)
AGA, n (%)	75 (77.3%)
Birth weight z-score	
<-2, n (%)	12 (12.4%)
≥-2, n (%)	85 (87.6%)
Sex	
Male, n (%)	51 (52.6%)
Female, n (%)	46 (47.6%)
5-minute Apgar score	
< 7, n (%)	10 (10.4%)
> 7, n (%)	86 (89.6%)
EUGR	
Yes, n (%)	40 (41.2%)
No, n (%)	57 (57.8%)
Necrotizing enterocolitis, n (%)	2 (2.1%)
Predominant feeding protocol	
MBM, n (%)	10 (10.3%)
MBBM, n (%)	75 (77.3%)
Formula, n (%)	12 (12.4%)

SGA, small for gestational age; AGA, adequate for gestational age; EUGR, extrauterine growth restriction; MBM: milked breastmilk; MBBM, milk bank breastmilk.

Binary logistic regression analysis (Enter variables input method) using as an outcome the diagnosis of EUGR employed the following variables: birth weight, calorie quota, birth weight z-score, bronchopulmonary dysplasia, late sepsis, length of NICU stay, and use of mechanical ventilation. Length of hospital stay and mechanical ventilation use were not included due to the presence of multicollinearity. The model was significant and well-fitted [X^2 (9) = p<0.001, R^2 Negelkerke = 0.469, Hosmer and Lemeshow test = 0.18, the percentage correct in the final classification table was 76.3%]. Of the

Table 2. Analysis of associations between quantitative variables and extrauterine growth restriction of 97 very low birth weight newborns admitted to a Neonatal Intensive Care Unit in Natal/RN, Brazil, from October 2017 to September 2018.

Variables	EUGR		No EUGR		*p*-value	CI (95%)	
	mean (± dp)	median	mean (± dp)	median		Lower	Upper
Birth weight, grams[a]	1122,7 (±246)	1145	1229 (±117,8)	1240	0,045	..	..
Weight at discharge, grams[b]	2024 (±259,3)	1950	2096,5 (±290,6)	2015	0,21	-186	42
Birth weight z-score[b]	-1,06 (±0,86)	1,07	-0,32 (±0,97)	0,00	<0,001	-1,12	-0,36
Discharge weight z-score[b]	-2,92 (±0,98)	-2,62	1,44 (±0,68)	-1,53	<0,001	-1,81	1,14
Difference in z-scores at discharge and birth[b]	1,85 (±1,04)	1,60	1,12 (±0,69)	1,22	<0,001	0,38	1,08
Time to regain birth weight, days[b]	13,0 (±4,5)	12	13,8 (±4,06)	13	0,14	-2,68	1,02
Use of parenteral nutrition, days[b]	12,8 (±7,3)	13	11,4 (±5,91)	12	0,30	-1,27	4,08
Full enteral nutrition, days[b]	17,6 (±10,4)	15	15,1 (±6,69)	14	0,14	-0,90	6,07
Calorie intake (PN+EN), kcal/kg/d							
1st week after birth[b]	60,8 (±15,8)	61,8	67,2 (±12,3)	67,8	0,03	12,1	-0,56
7-27 days after birth[b]	97,0 (±16,1)	98,1	101,6 (±12,3)	101,7	0,17	-11,4	-2,18
Protein intake (PN+EN), g/kg/d							
1st week after birth[b]	2,58 (±0,66)	2,73	2,77 (±0,51)	2,84	0,12	-0,43	0,52
7-27 days after birth[b]	2,89 (±0,48)	2,94	2,99 (±0,44)	3,03	0,32	-0,32	-0,10
Use of MV, days[a]	16,3 (±21,1)	7	7,89 (±11,6)	3,0	0,014	..	..
NICU stay, days[a]	41,1 (±27,1)	34,5	28,7 (±19,2)	23	0,006	..	..
Hospital stay, days[a]	61,5 (±26,9)	56,5	49,1 (±18)	47	0,021	..	..

EUGR: extrauterine growth restriction, 95%CI: 95% confidence interval, SD: standard deviation, PN, parenteral nutrition; EN, enteral nutrition; MV, mechanical ventilation, NICU, neonatal intensive care unit. [a]Mann-Whitney test; [b]Student's t-test.

Table 3. Analysis of associations between categorical variables and extrauterine growth restriction of 97 very low birth weight newborns admitted to a Neonatal Intensive Care Unit in Natal/RN, Brazil, from October 2017 to September 2018.

Variables	EUGR		No EUGR		*p*-value	OR	CI (95%)	
	n	%	n	%			Lower	Upper
Birth weight								
SGA (<10th percentile)	13	59.1	9	40.9	0.053	2.56	0.97	6.78
AGA (between 10th and 90th percentile)	27	36	48	64		1		
Birth weight z-score								
< -2	7	58.3	5	41.7	0.199	2.20	0.64	7.53
≥ -2	33	38,8	52	61.2		1		
Use of MV								
Yes	32	48.5	34	51.5	0.020	3.09	1.16	8.19
No	7	23.3	23	76.7		1		
Late sepsis								
Yes	29	54.7	24	54.7	0.003	3.62	3.62	8.65
No	11	25	33	75		1		
Full enteral nutrition (days)								
≤14 days	16	33.3	32	66.7	0.122	1		
>14 days	23	48.9	24	51.1		0.52	0.22	0.19
Bone metabolic disease								
Yes	28	47.5	31	52.5	0.104	2.05	0.85	4.94
No	11	30.6	56	58.9		1		
Bronchopulmonary dysplasia								
Yes	19	55.9	15	44.1	0.031	2.53	1.07	5.96
No	21	33.3	42	66.7		1		

EUGR: extrauterine growth restriction, *Odds Ratio*; CI (95%), 95% confidence interval, SGA, small for gestational age; AGA, adequate for gestational age; MV, mechanical ventilation. Used test: chi-squared.

variables analyzed, only birth weight z-score (p<0.001; OR = 0.18; 95% CI = 0.08-0.41) and use of mechanical ventilation (p = 0.006; OR = 11.2; 95% CI = 1.97-63.7) remained associated with EUGR, with birth weight z-score as a protective factor; the higher this score, the lower the risk of EUGR. The results are presented in Table 4.

DISCUSSION

Extrauterine growth restriction is a frequent and significant problem among all very low birth weight newborns, with prevalence ranging between 28 and 97% in this population[18]. In our study, 41.2% of the preterm infants had EUGR, a percentage considered significant due to the implication of this outcome with worse short and long-term outcomes.

Barreto (2013) performed a cross-sectional study in Rio Grande do Norte at the same institution. The author included 112 VLBW preterm infants and found that 89.3% of the preterm infants discharged from the hospital had EUGR[19]. In our study, the observed percentage of EUGR was lower; however, it is worth noting that in the first study the use of parenteral nutrition and breastmilk fortification was not common; in addition, another chart was used to monitor the growth of preterm infants, which tended to categorizing more patients as having EUGR[20].

A retrospective review by Clarck et al. (2003) using an administrative database with over 24,000 preterm infants from 124 NICUs managed by the Pediatrix Medical Group, Inc (Florida, USA) showed that 28%, 34%, and 16% of the patients had EUGR for weight, length, and head circumference, respectively[9]. In New Zealand, a prospective observational study of 293 infants, 104 of whom preterm infants, reported a decline in nutritional status during hospital stay with the proportion of preterm infants diagnosed with significant acute malnutrition increasing from 14% to 32% from admission to discharge[21].

There is evidence that the incidence of EUGR increases as birth weight decreases, since smaller preterm infants tend to lose more weight and take longer to regain birth weight[22,23]. In our study, lower birth weight infants had more significant growth restriction, although there were no significant differences in time to regain weight. Similarly, having a lower z-score at birth was the variable that showed the highest association with EUGR in binary logistic regression, a common finding in studies about growth restriction occurring in greater or lesser magnitude.

Decreases in the z-score from birth onwards, regardless of intensity, may lead to or worsen growth restriction[24]. In our study, we found a decrease of at least 1 point in the mean difference in z-scores from birth to discharge, which was higher in infants who developed EUGR (1.85 ± 1.04). Ávila-Alvarez et al. (2018) conducted a retrospective study which included VLBW newborns seen at a neonatal unit and found similar results. There was a 1-point decrease in the mean z-score for weight and length at discharge in all 130 infants included in the study during their stay in hospital[24]. A multicenter study organized by García-Muñnoz Rodrigo analyzed the patterns of weight gain after birth in a cohort of 4520 newborns with gestational ages at birth < 28 weeks and found that scores had decreased by -1.7[25].

Inadequate nutrition in these infants is a risk factor for the development of EUGR, especially in the first weeks after birth, a period when the brain is still developing, resulting in lower numbers of brain cells and deficits in behavior, memory, and learning[19,22,26]. Studies show that adequate energy and protein intake in the first week after birth is associated with better growth and neurological outcomes[19,22,23,26]. Thus, it is recommended to start nutritional support as early as possible, combining parenteral and enteral nutrition and optimizing energy and protein intakes[5].

Although there were no significant differences in the two groups regarding protein intake in the first week after birth, the higher energy intake by children without EUGR contributes to this outcome, since adequate energy intake is required to avoid impairment of amino acid and protein metabolism and consequently lean mass formation[26]. A study conducted in three NICUs in Toronto, from October 2010 to December 2012, aiming to describe the energy and macronutrient intake via enteral and parenteral nutrition in relation to the most current recommendations for aggressive nutrition, showed that with early and optimized nutritional support there was higher energy and nutrient intake; however, 34% and 71% of the VLBW infants did not meet the recommendations for protein and energy, respectively[26].

Table 4. Final binary logistic regression model for extrauterine growth restriction of 97 very low birth weight newborns admitted to a Neonatal Intensive Care Unit in Natal/RN, Brazil, from October 2017 to September 2018.

Variables	Unadjusted *p*-value	Unadjusted OR	Adjusted *p*-value	Adjusted OR	95% CI	
					Lower	Upper
Birth weight	0.045		0.55	1.00	0.99	1.00
Caloric quota	0.030		0.18	0.97	0.93	1.01
Birth z-score	< 0.001		<0.001	0.18	0.08	0.41
Bronchopulmonary dysplasia	0.031	2.53	0.21	3.01	0.53	16.9
Late sepsis	0.003	3.62	0.10	2.85	0.80	10.1
Length of NICU stay	0.006		0.98	1.00	0.96	1.03
Use of MV	0.020	3.09	0.006	11.2	1.97	63.7

OR: *odds-ratio*, 95% CI: 95% confidence interval, NICU: neonatal intensive care unit, MV: mechanical ventilation.

Growth deficits are often not directly related to nutritional support. VLBW infants present with specific comorbid conditions of prematurity that cause stress and inflammation in the body and thus increase catabolism, interfering with anabolic processes and growth[23,26,27].

In our study, need for ventilatory support, a situation that causes metabolic stress, was associated with EUGR. Infants with growth restriction used mechanical ventilation for twice as many days (median = 7) as infants without growth deficits (median = 3); moreover, use of mechanical ventilation was one of the variables that remained associated with EUGR in logistic regression. In preterm infants, the use of ventilatory support is often accompanied by lung and systemic inflammation due to high oxygen concentrations, resulting in metabolic stress[23].

Bose, Erhenkranz, et al. (2013)[27], carried out a study with 726 infants with gestational ages < 28 weeks and explored the relationship between mechanical ventilation and systemic inflammation. Their results show the presence of inflammatory proteins in the second week after birth, suggesting that systemic inflammation may begin soon after the introduction of mechanical ventilation and tends to increase with prolonged exposure, causing damage to other organs.

Mechanical ventilation may cause bronchopulmonary dysplasia and increase the likelihood of malnutrition as the energy that should be used for growth is spent with the infant's respiratory needs[27,28]. These infants spend high amounts of energy to maintain their metabolic rate, breathing pattern, thermoregulation, and synthesis of new tissue. In addition, it is common for infants in this situation to be prescribed fluid restrictions and to be given drugs that interfere with nutrient intake and absorption[28,29]. On the other hand, postnatal nutrition can affect lung development and the incidence of bronchopulmonary dysplasia, as suggested by Mataloun et al. (2009). In this study, the authors demonstrated that in preterm rabbits the reduction in the number of alveoli and collagen and elastin fibers was intensified when malnutrition was associated with hyperoxia[30].

The use of certain medications may also result in adverse effects on growth and nutrient metabolism, such as corticosteroids that promote catabolism, diuretics that cause losses of calcium, phosphorus and sodium important for muscle and bone development, and antibiotics that cause intestinal dysbiosis leading to poor digestion and nutrient absorption.[23] In our study, the incidence of EUGR was also higher in infants prescribed corticosteroids after birth, although without statistical significance. A larger sample size would be needed to confirm this association.

The small sample size is a limitation of the study, which hindered the association of the variables analyzed with the outcome studied. Only two associated factors were identified in multivariate analysis. However, since this is a prospective cohort study, it has positive characteristics for allowing follow-up over time, resulting in more accurate data.

Extrauterine growth restriction is still a problem observed in VLBW infants, with poorer nutritional status at birth and use of mechanical ventilation as the main factors for its development. Thus, it is necessary to improve postnatal nutritional support, adequately monitor growth, watch for clinical and nutritional factors that may interfere with it, and try to reduce the use and duration of mechanical ventilation in preterm infants, especially in the ones with lower birth weight and z-score at birth, in order to reduce short and long term complications.

Furthermore, it is extremely important that more attention be paid to prenatal care, through prevention, early identification, and appropriate intervention is provided to pregnant women at risk of preterm delivery and fetuses presenting intrauterine growth restriction, in order to reduce the birth of children with more compromised nutritional status.

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