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Prevalence of Extrauterine Growth Restriction and Associated Risk Factors in Newborns Weighing Less than 1500 Grams in a Neonatal Intensive Care Unit in Bogotá – Colombia

Prevalencia de la restricción de crecimiento extrauterino y factores de riesgo asociados en recién nacidos con peso menor de 1500 gramos en una unidad de cuidado intensivo neonatal de Bogotá (Colombia)

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ABSTRACT

Introduction: Newborns weighing less than 1500 grams present extrauterine growth restriction (EUGR) at hospital discharge in 40% to 90% and this is associated with increased morbidity. **Objective**: To describe the prevalence of EUGR and associated risk factors in newborns weighing less than 1500 grams at birth. **Methods**: Cross-sectional study with analytical component, which included neonates weighing less than 1500 grams, born in the institution between December 2015 and June 2020. **Results**: 128 patients with birth weight of 1,216 ± 207.8 grams and gestational age of 30 ± 2.3 weeks were identified. At hospital discharge 44.5% had EUGR, 56.1% of which were born with low weight for gestational age; 27/57 were classified as EUGR in severe category; 22.7% required pulmonary surfactant at birth and 84.2% presented bronchopulmonary dysplasia. **Conclusions**: The prevalence of EUGR at discharge in our unit is high and higher in low birth weight neonates who were 10 times more at risk. The use of surfactant was a protective factor.

Keywords

extrauterine growth restriction; postnatal growth retardation; very low birth weight.

RESUMEN

Introducción: Los recién nacidos con menos de 1500 gramos presentan una restricción de su crecimiento extrauterino (RCEU) al alta hospitalaria en un 40 % a un 90 % de los casos y ello se asocia con una mayor morbilidad. **Objetivo**: Describir la prevalencia de RCEU y los factores de riesgo asociados en recién nacidos con un peso menor de 1500 gramos al nacer. **Métodos**: Estudio de corte transversal con componente analítico que incluyó a los neonatos con peso menor de 1500 gramos nacidos en la institución entre diciembre de 2015 y junio de 2020. **Resultados**: Se identificaron 128 pacientes con peso al nacer de 1216 ± 207,8 gramos y edad gestacional de 30 ± 2,3 semanas. Al alta hospitalaria, el 44,5 % tenían RCEU, y de ellos el 56,1 % nacieron con bajo peso para la edad gestacional; el 47,4 % se clasificaron como RCEU en categoría grave; el 22,7 % requirió surfactante pulmonar al nacer, y el 84,2 % presentó displasia broncopulmonar. **Conclusiones**: La prevalencia de RCEU al alta en la población de estudio es elevada y mayor en los neonatos con bajo peso al nacer, quienes tuvieron 10 veces más riesgo. El uso de surfactante fue un factor protector.

Palabras clave

restricción del crecimiento extrauterino; retardo del crecimiento posnatal; muy bajo peso al nacer.

Introduction

Extrauterine growth restriction (EUGR) is defined as a weight less than the 10th percentile for corrected gestational age at 36 weeks or hospital discharge (1,2). Despite technological advances and the achievements of neonatology in terms of nutrition, infants weighing less than 1500 grams present EUGR in 40-90% of cases at hospital discharge and there is an inverse correlation between incidence and gestational age (2,3). Most infants who experience EUGR at birth have normal weight for gestational age, indicating that intrauterine growth was adequate, but lag behind overall growth during their hospitalization (4). Growth retardation is associated with poor neurodevelopmental and growth outcomes at 18-24 months (5), increased risk of developing respiratory disease after discharge, and complications such as hypertension, coronary, metabolic and endocrine diseases (6). All of this affects the quality of life of the patient and the family and represents costs to the health system and productivity in economic terms. EUGR continues to be a serious problem in preterm newborns, and there are few publications on the subject in our country.

Our hospital is a public tertiary care center with a high rate of premature births, with a high-risk population and which includes the most socially unprotected people, such as migrants. Therefore, we designed this study to determine the incidence of EUGR in the unit and the factors influencing EUGR in infants weighing less than 1500 grams at birth. The results will help us to design interventions to improve postnatal growth in the short and long term.

Materials and methods

This was a cross-sectional study with an analytical component in infants with a birth weight of less than 1500 grams, born in the neonatal intensive care unit (NICU) of Hospital Público Simón Bolívar de Bogotá (Colombia), over a five-year period (December 2015-June 2020). Data were collected retrospectively from a clinical database for newborns weighing less than 1500 grams. These data came from a single hospital.

The unit in which the study was conducted has a standardized nutritional management protocol for preterm newborns, which generally complies with current recommendations (7,8): amino acids in the first hours of life with the initiation of parenteral nutrition from day 0-1; initial protein intake of 3-3.5 g/kg each day, and daily caloric intake of 50-75 kcal/kg, with a target of 3.5-4 g/kg per day of protein and 110-120 kcal/kg at the end of the first week; initiation of early trophic enteral feeding; discontinuation of parenteral feeding once the preterm infant tolerates 100 ml/kg per day by enteral route, and fortification of breast milk. During the study period, no banked breast milk was available, so in the absence of breast milk, the preterm formula was used. There were no relevant changes in this protocol during the study period.

Somatometry variables (weight, length, and head circumference) were collected in absolute value and converted to *z*-scores or percentiles concerning the Fenton 2013 tables (9) and recorded at admission, NICU discharge, and hospital discharge. Low birth weight for gestational age was defined as birth weight below the 10th percentile (<P10). To calculate the rate of weight gain between 2 periods, the exponential method was used, with the following formula: rate of weight gain = (1000 × [final weight / initial weight])/number of days. At hospital

discharge, EUGR was classified according to z-scores as mild when greater than 1 and as severe when greater than 2 (5,9).

In addition, sociodemographic and clinical characteristics of the study group are reported. The presence of 4 or less with onset after the first trimester was considered poor prenatal care, and acceptable above this figure (10). As a marker of bronchopulmonary dysplasia, oxygen dependence at 28 days was collected. The sepsis registry was based on the clinical estimation of the treating physicians since microbiological isolation was minimal, but the registry by diagnosis was high.

A sample size of 128 patients allowed estimation of the incidence of malnutrition as a function of weight (<P10) for their gestational age at hospital discharge, with a confidence level of 95% and a precision of ±7%, for an expected proportion of 75%.

Analysis plan

Frequencies and percentages were used for qualitative variables; for quantitative variables, measures of central tendency and dispersion were determined. Bivariate analysis was estimated with odds ratios (ORs) and confidence intervals. On the other hand, Pearson's chi-square test (χ^2) and Fisher's exact test were used to evaluate the dependence between categorical variables; while the normality of quantitative variables was analyzed with the Kolmogorov-Smirnov test. Finally, Student's t-test and the Wilcoxon and Mann-Whitney rank tests were used to identify differences between means and medians in quantitative variables. Data were tabulated in Microsoft Excel, statistical analysis was performed in SPSS (version 26) and graphs were designed in R-Studio.

Results

During the review time analyzed, 221 babies were born weighing less than 1500 grams, of which 55 (24.88%) were excluded because they died during hospitalization, 5 were born in another institution, one had a major malformation, and 44 neonates whose medical records could not be located or was incomplete. Finally, 128 patients were included. The prevalence of extrauterine growth restriction at discharge was 44.5% (n = 57).

The sample was predominantly male (50.8%), 44.5% of the neonates had a gestational age between 25 and 29 weeks, and the mean weight of the newborns was 1216 ± 207.8 grams (Table 1).

Table 1
Demographic, clinical and somatometric characteristics of the patients included in the study

Variable	n = 128	%	Mean ± SD	Min-Max
Sex				
Male	65	50.8		
Female	63	49.2		
Gestational age			**30.01 ± 2.36**	**24-37**
25-29	57	44.5		
30-32	51	39.8		
33-36	19	14.8		
≥37	1	0.8		
Health system affiliation regime				
Subsidized	97	75.8		
Contributory	31	24.2		
Prenatal care			**2 ± 2.1**	
None	23	17.9		
Poor (≤4)	76	59.4		
Acceptable	28	21.9		
Maternal age			**26.5 ± 6.1**	**16-40**
Parity			2.1 ± 1.29	1-7
Type of gestation				
Single	108	84.4		
Multiple	20	15.6		
Maternal nutritional status				
Normal Weight	84	65.6		
Underweight	9	7.0		
Undernourished	1	0.8		
Overweight	25	19.5		
Obese	9	7.0		
Birth weight (grams)			**216.6 ± 207.8**	**580-1495**
<600	1	0.8		
600-800	2	1.6		
801-1000	22	17.2		
1001-1200	25	19.5		
1201-1499	78	60.9		

Table 1 (cont.)
Demographic, clinical and somatometric characteristics of the patients included in the study

Variable	n = 128	%	Mean ± SD	Min-Max
Height at birth			38.7 ± 3.2	29-49
CP at birth			27.24 ± 1.8	22.5-33
Type of delivery				
Vaginal	32	25		
C-section	96	75		
Cause of the intervention				
Preeclampsia	47	36.7		
Nonreassuring fetal status	38	29.7		
Other	43	33.5		
Low Apgar at 5 minutes (<7)	3	2.3		
Surfactant requirement	84	65.6		
Need for resuscitation at birth	82	64.1		
Invasive ventilation	**81**	**63.3**	**6.5 ± 12.7**	**1-69**
≤24 h	75	58.6		
Prolonged ventilation (>7 days)	28	34.5		
Non-invasive ventilation	114	89.1	22.5 ± 18.05	1-78
Prenatal steroids	45	35.2		
Postnatal steroids	11	8.6		
Oxygen requirement (≥28 days)	117	91.4		
Classification of the newborn according to birth weight				
Adequate weight	88	68.8		
Underweight	40	31.3		
Percentage of weight loss in the first week			8.2 ± 3.8	1-18
IUGR	39	30.5		
EUGR	57	44.5		
Weight at NICU discharge			1973 ± 603	603-4020
Height at NICU discharge			44.8 ± 4.2	37-67
CP at NICU discharge			31.3 ± 2.7	24-42
Weight at hospital discharge			2788.3 ± 503.2	2405-4480
Height at hospital discharge			47.9 ± 3.5	33-58
PC at hospital discharge			33 ± 2.4	28-48
Days of NICU stay			71.3 ± 32	1-103
Days of hospital stay			61.19 ± 23.3	20-140
Gestational age at discharge			39 ± 2.8	34-47
Nutritional support				
Exclusive enteral	3	2.3		
Parenteral support time			14.64 ± 10.8	1-73
Early initiation of enteral feeding (<24 h)	61	47.7		
Exclusive breastfeeding	8	6.2		
Mixed	120	93.8		
Age to complete enteral feeding			14.64 ± 10.8	
Use of fortifier	120	93.8		

The mean maternal age at delivery was 26.5 years, with 2.1 gestations, with normal weight (65.6%). Abdominal delivery prevailed (96 cesarean sections vs. 32 vaginal), whose indication was preeclampsia in 36.7% of cases; nonreassuring fetal status in 29.7%, and other causes in 33.5%, which included preterm labor and placental abruption. 77.3% of the pregnancies had had poor prenatal care (≤4), 23 of which had no prenatal care at all. 75.8% belonged to the subsidized health system, which corresponds to the population without labor affiliation and under the responsibility of the State.

Within the EUGR cohort, there was a greater need for resuscitation (82%), requiring at least one cycle of positive pressure ventilation. Three of these patients presented low Apgar (<7) at 5 minutes, without asphyxia. All patients had an indication for intensive care at admission, and 63.3% required invasive ventilatory support, with 58.6% requiring less than 24 hours and 34.5% of patients requiring prolonged ventilation (>7 days). Eleven of the latter required a course of postnatal steroid for extubation. The mean number of days of hospitalization in the NICU was 34.9, and the mean length of hospital stay was 61.3, with a mean gestational age at the discharge of 39 ± 2.8 weeks.

The main complications documented in the study group were: bronchopulmonary dysplasia (91.4%) and sepsis classified by clinical criteria (60.2%). Thirty-nine percent of patients presented cerebral hemorrhage, 90% of which were mild (grades I and II). The bone disease of prematurity was associated with 21.9% of patients. Ten patients were complicated in their evolution with necrotizing enterocolitis, and of these 3.1% had short bowel syndrome (Table 2).

Table 2
Major complications

Variable	n = 128	%
Bronchopulmonary dysplasia	117	91.4
Extrauterine growth restriction	57	44.5
Sepsis	77	60.2
Respiratory distress syndrome	52	40.6
Cerebral hemorrhage	50	39
Mild (Grade I y II)	45	90
Grade III	4	8
Grade IV	1	0.8
Osteopenia	28	21.9
Arterial hypertension	16	12.5
Necrotizing enterocolitis	10	7.8
Significant ductus	10	7.8
Pharmacological closure	9	90
Surgical closure	1	10
Pulmonary hypertension	6	4.6
Retinopathy	5	3.9
Short bowel	4	3.1
Hydrocephalus	4	3.1

Hemodynamic repercussions were observed due to the persistence of the ductus, with no response to general measures (including water restriction) in 10 patients, 9 of whom required pharmacological closure (7.8%) with a course of intravenous ibuprofen. One patient required surgical management. Of the 128 patients, five developed retinopathy (3.9%), and one of them required surgical management, with a good response.

In the present distribution according to birth weight, a maximum representation of 49.20% (n = 63) was observed for patients with adequate weight, and a minimum, with a percentage of 6.30% (n = 8), for those underweight (Table 3).

Table 3
Factors associated with extrauterine growth restriction

Variable	Extrauterine growth restriction at discharge				OR	IC95		*p*
	Yes		No			Lower limit	Upper limit	
	n	%	n	%				
Maternal-related								
Maternal nutritional status								
Undernutrition	1	0.80	0	0.00	---	---	---	0.78
Underweight	4	3.10	5	3.90				
Normal weight	36	28.10	48	37.50				
Overweight	11	8.60	14	10.90				
Obesity	5	3.90	4	3.10				
Undernutrition and underweight								
Yes	5	3.90	5	3.90	1.27	0.35	4.62	0.75
No	52	40.60	66	51.60				
Overweight and obesity								
Yes	16	12.50	18	14.10	1.15	0.52	2.52	0.73
No	41	32.00	53	41.40				
Health system affiliation regime								
Subsidized	45	35.20	52	40.60	1.37	0.6	3.13	0.45
Contributory	12	9.40	19	14.80				
Pregnancy-related								
Type of pregnancy								
Multiple	7	5.50	13	10.20	0.62	0.23	1.69	0.35
Single	50	39.10	58	45.30				
Parity								
1	26	20.30	24	18.80	---	---	---	0.45
2	13	10.20	22	17.20				
3	8	6.30	15	11.70				
4	6	4.70	6	4.70				
5	4	3.10	2	1.60				
6	0	0.00	1	0.80				
7	0	0.00	1	0.80				

Table 3 (cont.)

Factors associated with extrauterine growth restriction

Variable	Extrauterine growth restriction at discharge				OR	IC95		p
	Yes		No			Lower limit	Upper limit	
	n	%	n	%				
Prenatal care								
No care	10	7.80	14	10.90	---	---	---	0.9
Poor (≤4)	44	34.4	56	43.8		0.90	0.39	2.10
Acceptable (>4)	13	10.2	15	11.7				0.819
Delivery route								
C-section	44	34.40	52	40.60	1.24	0.55	2.78	0.61
Vaginal	13	10.20	19	14.80				
Newborn-related								
Sex								
Male	31	24.20	34	26.60	1.3	0.65	2.61	0.46
Female	26	20.30	37	28.90				
Classification according to birth weight								
Underweight	32	25.00	8	6.30	10.08	4.09	24.86	<0.001**
Adequate weight	25	19.50	63	49.20				
Prenatal steroid use								
Yes	21	16.40	24	18.80	1.14	0.55	2.37	0.72
No	36	28.10	47	36.70				
Postnatal steroid use								
Yes	7	5.50	4	3.10	2.35	0.65	8.45	0.18
No	50	39.10	67	52.30				
Neonatal intensive care unit requirement								
Yes	30	23.40	9	7.00	7.65	3.2	18.29	<0.001**
No	27	21.10	62	48.40				
Supplemental oxygen requirement at 28 days								
Yes	48	37.50	69	53.90	0.15	0.03	0.75	0.011*
No	9	7.00	2	1.60				

Table 3 (cont.)

Factors associated with extrauterine growth restriction

Variable	Extrauterine growth restriction at discharge				OR	IC95		p
	Yes		No			Lower limit	Upper limit	
	n	%	n	%				
Newborn-related								
Pulmonary hypertension								
Yes	2	1.60	4	3.10	0.61	0.11	3.45	0.69
No	55	43.00	67	52.30				
Neonatal cerebral hemorrhage								
No	32	25.00	46	35.90	-	-	-	0.45
Grade I	19	14.80	20	15.60				
Grade II	4	3.10	2	1.60				
Grade III	1	0.80	3	2.30				
Grade IV	1	0.80	0	0.00				
Patent ductus arteriosus								
No	49	38.30	69	53.90	-	-	-	0.06
Pharmacological closure	7	5.50	2	1.60				
Surgical closure	1	0.80	0	0.00				
Short bowel syndrome								
Yes	3	2.30	1	0.80	3.89	0.39	39.44	0.32
No	54	42.20	70	54.70				

Table 3 (cont.)
Factors associated with extrauterine growth restriction

Variable	Extrauterine growth restriction at discharge				OR	IC95		p
	Yes		No			Lower limit	Upper limit	
	n	%	n	%				
Newborn-related								
Enterocolitis								
Yes	4	3.10	6	4.70	0.82	0.22	3.05	1
No	53	41.40	65	50.80				
Surgery for enterocolitis								
Yes	4	3.10	2	1.60	2.6	0.46	14.76	0.41
No	53	41.40	69	53.90				
Nutritional support								
Enteral	0	0.00	3	2.30	-	-	-	0.23
Parenteral	3	2.30	2	1.60				
Mixed	54	42.20	66	51.60				
Enteral feeding start time								
Late	33	25.80	34	26.60	1.5	0.74	3.02	0.26
Early (before 24 hours)	24	18.80	37	28.90				
Fortifier								
Yes	54	42.20	66	51.60	1.36	0.31	5.97	0.73
No	3	2.30	5	3.90				
Surfactant								
Yes	29	22.70	55	43.00	0.3	0.14	0.65	0.001**
No	28	21.90	16	12.50				
Retinopathy of prematurity								
Yes	3	2.30	2	1.60	1.92	0.31	11.88	0.66
No	54	42.20	69	53.90				

*Statistically significant at 0.05.
**Statistically significant at 0.01.

For the variable NICU requirement, the maximum percentage was 48.40% (n = 62) and the minimum percentage was 7% (n = 9); there was no EUGR at discharge in either group. In the surfactant variable, the maximum percentage was 43% (n = 55), and the minimum was 12.50% (n = 16). Restriction was not evident in any group of patients. Regarding supplemental oxygen requirement at 28 days of life, the maximum percentage was 53.90% (n = 69) compared to a minimum percentage of 1.60% (n = 2); no EUGR was present in either group at discharge.

In the time to initiation of enteral feeding, there was a maximum percentage of 28.90% (n = 37) for neonates who received enteral feeding before 24 hours of life without restriction, compared to a minimum percentage of 18.80% (n = 24) for patients treated with a time fewer than 24 hours with the presence of restriction. After this, a maximum percentage of 51.60% (n = 66) was analyzed for the fortifier variable with the absence of restriction compared to the minimum percentage of 2.30% (n = 3) for patients treated with the presence of restriction.

Finally, for the variable retinopathy of prematurity, there was a maximum percentage of 53.90% (n = 69) and a minimum percentage of 1.60% (n = 2) for patients treated with no extrauterine growth restriction at discharge.

A statistically significant association was found with the occurrence of EUGR at discharge in cases where neonates required surfactants (OR = 0.30; 95%CI = 0.14-0.65; p = 0.001), with birth weight classification (OR = 10.08; 95%CI = 4.09-24.86; p < 0.001), with NICU requirement (OR = 7.65; 95%CI = 3.20-18.29; p < 0.001), and with oxygen requirement (OR = 0.15; 95%CI = 0.03-0.75; p = 0.011).

Evolution of the newborn with extrauterine growth restriction

When evaluating the evolution of weight from birth to hospital discharge, it was found that there was an average increase of 13.86 percentage points in the proportion of neonates weighing less than P10 (Figure 1).

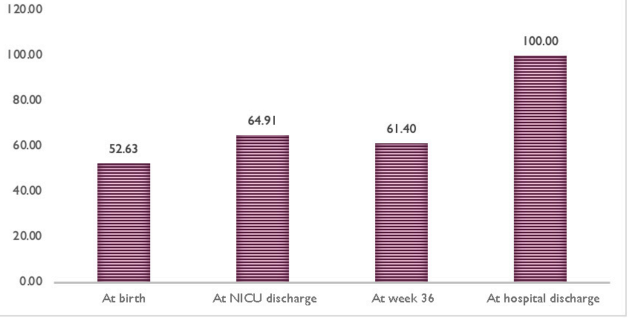

Figure 1
Proportion of EUGR neonates weighing <P10 from birth to hospital discharge

Of the total number of patients with EUGR at discharge, 47.3% were classified in the severe category (>2 decrease in z-score at discharge).

When comparing the rate of weight gain (g/kg per day) between hospitalization stages (birth-to-NICU discharge and NICU discharge-to-hospital discharge) in patients with EUGR, it was found that from birth to NICU discharge neonates with severe EUGR had a median of 28.5, compared with a median of 27.65 for those with mild EUGR, i.e., a median ratio of 1.03. Meanwhile, from NICU discharge to hospital discharge, the median for those with severe EUGR was 17.6, compared to those with mild EUGR, 21.7 (Figure 2). When comparing the medians of both moments using the Mann-Whitney U test, there were no statistically significant differences (Table 4).

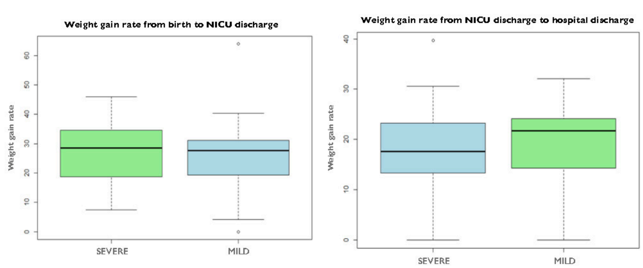

Figure 2
Comparison between weight gain rate distributions (g/kg per day) for each stage of hospitalization

Table 4
Comparison of weight gain rates by stage of hospitalization

Weight gain rate (g/kg per day)	Degree of EUGR: Severe**		Mild		Median ratio	p^*
	Median	IQR	Median	IQR		
From birth to NICU discharge	28.5	20.2	27.65	11.8	1.03	0.477
From NICU discharge to hospital discharge	17.6	10.4	21.7	9.8	0.81	0.397

*Mann-Whitney U.
**Reference category for the median ratio.

Finally, when evaluating the recovery of birth weight in the first week, it was identified that 71.92% (n = 41) of the neonates with EUGR recovered weight, while the remaining 28.07% (n = 16) did not.

Discussion

Preterm newborns represent the highest percentage of patients hospitalized in the NICU of our hospital. According to national and international trends in neonatal care, survival is higher at lower gestational age. However, there is a high incidence of EUGR at hospital discharge. There are few publications on the subject in Colombia. In the study population, 44.5% of preterm infants with birth weight less than 1500 grams had EUGR at discharge, lower than the national report in two institutions in Bogota (4) of 73%, between 2014 and 2015, but higher than that found in developed countries.

Clark et al., cited in Ruiz Castro et al. (4), analyzed 24,371 preterm infants with a gestational age of 23 to 34 weeks hospitalized in 127 units in the United States. At discharge, infants were assessed for weight, length, and head circumference, and the incidence of EUGR based on these measures was 28. Radmacher et al. (11) retrospectively analyzed 199 infants with birth weight ≤1000 grams and gestational age ≤29 weeks, and the incidence was 59.3%. In 2015, the collaborative group of the Nutrition Expert Committee of the Chinese Neonatal Professional Committee conducted a multicenter study on 572 very low birth weight infants in 15 hospitals across the country. The incidence of EUGR at discharge was 80.9 %, while 63.6 % had a birth weight below the P3 percentile (12). Cai Yueju et al. cited in Zhao et al. (13) found 26.1. The Xinjiang Hospital (China) published in April 2021 a study of the last 3 years, with 691 preterm newborns <34 weeks with 36.9% (13). This series of reports indicates that worldwide the incidence of EUGR in newborns weighing less than 1500 grams has decreased but remains high and requires attention in clinical practice.

It is possible that the reason why this group does not recover its growth channel may be multifactorial. Among maternal factors, preterm delivery is largely caused by gestational hypertension, especially preeclampsia-eclampsia, which can lead to maternal vasoconstriction, insufficient placental blood flow, low fetal nutritional reserve, and intrauterine growth restriction (14). Within the cohort, we found a higher frequency of emergent cesarean births, whose main cause was preeclampsia. In addition, requiring hospitalization in the NICU was a risk factor for EUGR.

The use of surfactant was found to be a protective factor for the occurrence of EUGR at discharge, a fact that may be related to the decrease in the requirement and time of invasive ventilation, in addition to the energy savings involved. On the contrary, for Sacchi et al. (15), the use of surfactants during hospitalization was associated with a motor development index lower than 85 (OR = 1.89; 95% CI = 1.04-3.44); we believe that more studies should be conducted to define this relationship.

Of note, our newborns with birth weights <P10 had a 10-fold increased risk of EUGR ($p < 0.001$). This supports the results of Zhao et al. (13) and Tyrrell et al. (16). In addition, Sacchi et al. (15), in a systematic review and meta-analysis involving 52,822 intrauterine growth-restricted and small-for-gestational-age children, indicated that they had significantly poorer cognitive outcomes than children with adequate weight for gestational age. These findings highlight the need to develop interventions that enhance cognitive functions in these high-risk groups.

Patients with a higher percentage of weight loss in the first week of life took longer to regain birth weight. 71.92% (n = 41) of our neonates with EUGR regained weight at 7 days of life. In addition, lower weight gain was found in the period from NICU discharge to hospital discharge, a result that may be related to the decrease in protein intake in the transition and full enteral feeding phase, and its determination requires further studies. In a retrospective review of 156 infants, Miller et al. (17) found that growth was impaired during the transition phase, related to decreased protein intake ($p < 0.0001$). Serum urea nitrogen also decreased and correlated with the intake of these ($r = -0.32$; $p < 0.001$). Insufficient growth during the transition phase makes infants 5 times more likely to be discharged with weights below PO10 for corrected gestational age; therefore, optimizing protein supply during parenteral nutrition weaning is an important strategy to prevent postnatal growth retardation (14).

Parenteral feeding is essential to maintain nutritional intake before a successful transition to the enteral route is achieved, and initially, trophic feeding is intended to mature the gastrointestinal tract. Hence, starting with breast milk facilitates this maturation and reduces the risk of enterocolitis and sepsis (7,17). Mother's own expressed breast milk is the milk of choice, and it is necessary to supplement it with a fortifier to optimize nutritional intake. Preterm formulas are an accepted substitute for breast milk when the latter option is not available (7,18).

The incidence of gastrointestinal diseases, such as necrotizing enterocolitis, was higher in the EUGR group than in the non-EUGR group. All patients who had enterocolitis started trophic stimulation with milk formula after 24 hours of life, due to instability and lack of availability of breast milk. This could be related to slow gastric emptying, duodenal reflux, prolonged intestinal transit, irregular bowel movements, lactase inactivity, and reduced digestion and absorption.

Bogota has only one human milk bank. The limitation of these banks increases the likelihood of starting enteral feeding with formula, which favors intolerance, greater episodes of suspension of supply, fasting, and a greater likelihood of necrotizing enterocolitis.

The literature is consistent in demonstrating that the administration of breast milk is associated with less necrotizing enterocolitis in the very preterm infant population. In fact, the two most effective methods to decrease the risk of enterocolitis are to be born at a mature gestational age and to increase breast milk intake (19,20).

Nutrition influences brain development and has a neuroprotective function. Gut microbiota can modulate brain function and maturation through immune signaling. There are more than

10 systematic reviews of randomized controlled trials published by the Cochrane Library that address the use of breast milk, its benefits, and feeding strategies (20).

Preterm infants with early onset of neonatal sepsis, respiratory disease, healthcare-associated infections, those requiring invasive ventilation, and those subjected to painful and stressful stimuli are in a state of high energy consumption and increased demand for calories and protein (21,22). Preterm infants, with the additional complication of respiratory disease and symptomatic patent ductus arteriosus, may also face restricted fluid intake, reduced nutrient intake, and severe negative nitrogen balance shortly after birth. These factors also increase the incidence of EUGR, and in the study, these factors did not show significant differences. Sepsis was recorded in 60.2% of our patients at some time during evolution, although it was more frequent after 72 hours of life. However, we did not consider this variable evaluable, because the diagnosis depended on the clinical assessment of the treating physician, and microbiological isolation in blood cultures was only reported in one patient.

Recent publications directly link sepsis to EUGR. Between 2006 and 2011, Flannery et al. (23) collected a series of 4875 infants younger than 32 weeks with birth weight less than 1500 grams at 29 neonatal centers in the United States and Canada and concluded that sepsis was associated with a greater decrease in weight *z*-score (mean difference -0.09; 95% CI = -0.14 to -0.03). Postnatal weight growth retardation (decreased weight *z*-score >1) was present in 237 (34 %) neonates. Length growth trajectories showed similar initial changes in weight *z*-scores between neonates with and without sepsis, but at 3 weeks after the onset of sepsis, there was a greater decrease in weight *z*-scores relative to birth values in those with sepsis than in those without sepsis (delta *z*-score of -0.89 vs. -0.77; mean difference: -0.12; 95% CI: -0,18 a -0,05). This significant difference persisted until 36 weeks or until discharge (22).

In Japan, Chien et al., cited in Flannery et al. (23), conducted a neurological follow-up of 224 very low birth weight infants at the corrected age of 24 months and established that sepsis was associated with cerebral palsy (OR = 4.53; 95%CI = 1.43-14.35). This aspect highlights the importance of adequate prenatal care and careful management of this population group in the NICU to reduce infections and their impact.

Conclusions

In the care of newborns, especially very low birth weight preterm infants, the consequences of EUGR on impaired linear growth, as well as on neurological, respiratory, cardiovascular and endocrinological development should be considered. To reduce the incidence of EUGR, clinical management should focus on providing early nutritional intake to avoid atrophy and gastrointestinal dysfunction, combined with optimal parenteral nutritional support, allowing infants to achieve an adequate growth rate (at least 18-20 g/kg per day), but avoiding overfeeding.

In the study unit, despite complying with current recommendations and standardization of nutritional management of premature infants, the lack of availability of human milk banks increases exposure to early initiation with formula, favors intolerance and the probability of enterocolitis, with an increase in fasting times and, therefore, of EUGR.

Given that this is a single-center study, the generalization of the results to other centers is limited. However, the homogeneity of the sample can strengthen the validity of the data.

There are few publications on the subject in our country, so future studies on a larger scale are required to clarify the discrepancy in the results between centers and plan better and uniform intervention strategies that will allow us to reduce the incidence of EUGR.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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