ORIGINAL RESEARCH

Extrauterine Growth Restriction in Preterm Very Low Birth Weight Infants: The Use of a Web-based System Designed for Computerized Prescribing of Parenteral Nutrition in Neonatal Intensive Care

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Abstract

Aim: Extrauterine growth restriction (EUGR) is a multifactorial condition that may lead to long-term consequences for preterm infants. Providing adequate nutrition is one of the keys to ameliorating growth. Technology can help clinicians with powerful tools. We evaluate the impact of a web-based software specifically designed for neonatal parenteral nutrition (PN) prescription on EUGR in a cohort of very low birth weight (VLBW) infants.

Materials and methods: We retrospectively analyzed anthropometric measurements (AMs) and comorbidities in a cohort of 119 VLBW infants treated with PN for at least 5 consecutive days. International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) standards were used to identify small for gestational age (SGA, birth weight < 10th centile) infants and to define EUGR. EUGR was defined as "cross-sectional" (AMs < 10th percentile at discharge) and "longitudinal" (loss in AMs *Z*-score from birth to discharge > 1 standard deviation [SD]).

Results: Nutritional intakes were consistent with current available nutritional guidelines. There were significant differences in the measured incidence of EUGR depending on the adopted definition. The longitudinal definition appeared to be the most appropriate than the cross-sectional one for identifying postnatal growth failure in preterm infants. Lower lipid intake and longer durations of PN were risk factors for poor growth in weight and head circumference (HC). Metabolic disorders, such as cholestasis, hyperglycemia, and hypertriglyceridemia, had stronger links with lower AMs and longer PN needs than just the nutritional intakes. No relationships were observed between the most of comorbidities associated with prematurity and EUGR.

Conclusion: A web-based system for the prescription of neonatal PN seems to be useful for ensuring adequate intakes in preterm infants. Further studies with larger sample sizes could be designed for evaluating the application of this software within a neonatal network and its effect on postnatal growth.

Clinical significance: The use of an electronic prescribing system designed for neonatal care can help neonatologists in giving VLBW infants the correct intake of nutrients.

Keywords: Computerized prescribing, Extrauterine growth restriction, Newborn, Parenteral nutrition.

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Introduction

Preterm very low birth weight (VLBW) infants are at risk of extrauterine growth restriction (EUGR), which has a potential impact on neurodevelopmental outcomes.[1–5] Several factors have been associated with EUGR, including male sex, small for gestational age (SGA) infants, comorbidities of prematurity, and nutritional intakes.[6,7] Guaranteeing optimal nutrition is one of the vital aspects in preterm VLBW infants to ensure adequate postnatal growth and organ development.[8,9] Because of the immaturity of the gastrointestinal system and the limited stores of nutrients,[10] preterm VLBW infants usually need parenteral nutrition (PN) in the first few weeks after birth life to achieve their nutritional requirements of energy, proteins, and lipids, until those can be achieved by full enteral feedings (FEF).[11–13]

In this setting, the use of a specific software dedicated to PN ordering could help to improve the prescription and the final product in many ways.[11,14,15] It could potentially reduce prescribing errors and compatibility and stability of the PN solutions.[16] These software tools could also guide prescribers to order appropriate nutrients and energy in relation to gestational and postnatal age.[14,17] This study aimed to evaluate the following: (a) The use of

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the web-based system,[18] Par/Ent®, for computerized prescription of PN in preterm VLBW infants; (b) the occurrence of EUGR in relation to demographic characteristics at birth, PN intakes and common co-morbidities of prematurity;[19] and (c) the frequency of complications in relation to PN intakes.[20]

Materials and Methods

This is a population-based study of preterm VLBW infants who were admitted to the Neonatal Intensive Care Unit of Children's Hospital, ASST Spedali Civili of Brescia, Italy, and received PN from the day of birth for at least five consecutive days. Data were retrospectively collected from March 2019 to October 2020. Exclusion criteria were death in the first 15 days of life, major congenital malformations, genetic syndromes, and delayed admission after the first day following birth.

PN was prescribed using the computerized web-based system, Par/Ent®, which was designed specifically for neonatal intensive care by Link Up, S.r.l of Italy, on behalf of the Italian Society of Neonatology. After entering the gestational age and weight of the infant into the program, the software suggests nutritional intakes per current guidelines.[21,22] It also provides functionalities for the following: (a) Integration between enteral and parenteral supplies through an algorithm that avoids the dispersion of nutrients and ensures correct overall intakes, (b) counting and appropriate scaling of drugs, (c) the use of separate lines for PN and for infusing blood components, and (d) evaluating the compatibility of nutrients and drugs with the PN bag. Once data are entered for enteral feeding, intravenously administered drugs, and transfusions of blood components, the system recalculates the doses of all components so that the total amount of liquids and nutrients remains as prescribed. Moreover, by choosing the prescription method called "recommended calculation," the system takes coefficients of intestinal absorption of the nutrients into account.[23] It also has a monitoring system that produces alerts in case of lipid emulsion instability, the enhanced risk for insoluble salt precipitates, and excessive osmolarity of the peripheral infusion.

Clinical and laboratory data were collected using the electronic healthcare applications, Milos 1.0 (Gruppo Finmatica, Italy) and Fenix OE (EL.CO. Italy), while daily intake and PN solutions data were collected using Par/Ent® database. Percentile and *Z*-scores for weight, length and head circumference (HC) were calculated using the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) international growth standards for newborn size and postnatal growth of preterm infants, at birth and at discharge, respectively.[24–26]

Small for gestational age was defined as a birth weight below the 10th percentile for gestational age.[27] To define EUGR, we used the following two definitions: (a) Weight, length, and HC below the 10th percentile at discharge, the "cross-sectional EUGR"[28] and (b) *Z*-scores[29] for weight, length, and HC loss between birth and discharge below 1 standard deviation (SD), the "longitudinal EUGR."[19,30] Infants were classified according to these definitions to be with- or without-EUGR for each measure. The following definitions for comorbidities of prematurity and PN complications were used: cholestasis was defined as a conjugated when the direct bilirubin levels were above 2 mg/dL when the total bilirubin was below 5 mg/dL, or if these levels were above 20% of total bilirubin levels higher than 5 mg/dL[31]; hypertriglyceridemia as serum triglycerides >250 mg/dL;[32] hyperglycemia as repeated blood glucose levels above 180 mg/dL that were treated with continuous insulin infusions;[33] hypophosphatemia as a serum phosphate level below 5 mg/dL; severe hypophosphatemia as serum phosphate levels below 3.1 mM; and hypercalcemia as serum calcium levels above 11 mg/dL.[34] Neonatal sepsis (symptomatic infants with a pathogen isolated from the blood culture) was classified as early-onset (EOS; <72 hours of life) or late-onset (LOS; >72 hours of life).[35] Necrotizing enterocolitis (NEC) was defined according to the Vermont–Oxford Network (VON) criteria (clinical and radiographic gastrointestinal signs).[36] We defined bronchopulmonary dysplasia (BPD; any severity) according to Jobe and Bancalari's original definition,[37] retinopathy of prematurity (ROP) using the International Classification of ROP guidelines,[38] and intra-ventricular hemorrhage (IVH) according to the criteria of Papile et al.[39] Patent ductus arteriosus (PDA) was diagnosed when the echocardiography showed findings consistent with at least one of the following: Left to right shunt, bidirectional shunt, and systolic or continuous murmur, and these were detected in the contextual presence of above or equal to 2 of the clinical signs such as hyperdynamic precordium, palpitations, systemic arterial hypertension, pulmonary vascular congestion, and cardiomegaly.[40,41]

Demographic and clinical information data and nutritional intakes were analyzed using descriptive statistics.[42] Continuous variables were presented as the median and interquartile range (IQ) and were compared using the Mann–Whitney U test.[43] Categorical variables were presented as the frequency and percentage and were compared using Fisher's exact test.[44] To identify the association between multiple variables, logistic regression was used.[45] Statistical tests were considered significant for $p < 0.05$.[46] We used the software programs MedCalc for Windows (MedCalc Software, Mariakerke, Belgium) and Statistica for Windows (StatSoft, Inc., Tulsa, OK, USA) to analyze these data.[47]

Results

During our study period, we reviewed the case records of 133 VLBW infants who were treated with PN for at least 5 days at the NICU of Spedali Civili, Italy. Fourteen infants were excluded from the study cohort; the reasons were death during the first 15 days after birth ($n = 3$), congenital malformations ($n = 9$), transfer to another hospital within a few days after hospitalization ($n = 1$), and admission after the first day following birth ($n = 1$). A total of 119 infants were included in the study. Demographic characteristics of infants per the INTRERGROWTH-21st standards[24,25] are presented in Table 1.

Male sex was not associated with either cross-sectional or longitudinal EUGR for all definitions. The occurrence of EUGR for weight, length, and HC and its relationship with the demographic characteristics at birth are shown in Table 2. The cross-sectional definitions for weight and HC showed significantly higher frequencies for EUGR than the longitudinal definition. However, the occurrence of EUGR for length was similar between the two definitions. According to the cross-sectional definition, infants with EUGR for weight had a higher gestational age at birth than those without postnatal growth retardation. Extrauterine growth restriction infants according to the longitudinal definition for weight had a lower gestational age. Cross-sectional EUGR for length infants had birth weights and lengths lower than those without EUGR. Infants with longitudinal EUGR for length had lower gestational ages, birth weights, and HCs than those without EUGR. Cross-sectional EUGR for HC infants had lower birth weights, lengths,

Table 1: Demographic characteristics of infants according to INTERGROWTH-21st standards

Gestational age (weeks)	29.7	(27.8–31.7)
Female, number (%)	63	(53)
Birth weight (gm)	1129	(922–1335)
Birth weight *Z*-score	–0.82	(–1.70 to –0.08)
Birth weight percentile	20.5	(4.4–46.7)
SGA, number (%)	42	(35)
Birth lengths (cm)	37.5	(35.0–39.2)
Birth lengths *Z*-score,	–0.83	(–1.40–0.01)
Birth lengths percentile	20.3	(7.9–48.5)
Birth head circumference (cm)	26.0	(25.0–27.9)
Birth head *Z*-score	–0.86	(–1.65 to –0.32)
Birth head percentile	19.4	(4.9–37.1)
Lengths of stay (days)	54.0	(38.0–75.0)
Discharge PMA (weeks)	37.6	(36.2–39.5)
Discharge weight (gm)	2190	(2001–2703)
Discharge weight *Z*-score	–1.07	(–2.00 to –0.44)
Discharge weight percentile	13.5	(2.2–31.1)
Discharge length (cm)	45.0	(43.0–47.0)
Discharge length *Z*-score	–1.46	(–2.60 to –0.57)
Discharge length percentile	7.2	(0.5–28.2)
Discharge head circumference (cm)	32.0	(31.0–33.5)
Discharge HC *Z*-score	–0.77	(–1.99–0.10)
Discharge HC percentile	22.0	(2.3–54.0)

Values are expressed as number (%) and median (IQ). PMA, postmenstrual age

and HCs than those without EUGR. Infants with longitudinal EUGR for HC had lower gestational ages and birth weights than those without EUGR. The relationship between nutritional characteristics, including nutrients intake, and the occurrence of EUGR for weight, length, and HC are summarized in Tables 3 to 5.

Infants with postnatal growth retardation per the cross-sectional definition of EUGR had lower 7 days calcium/phosphate (C/P) ratios than the subgroup who did not have EUGR. Length- and HC-restricted infants had lower parenteral lipid intakes. When the longitudinal EUGR definition was applied, weight- and length-restricted infants showed longer durations of PN than those without EUGR, with consequent delay in the achievement of FEF. Length- and HC-restricted infants were also more likely to have received less parenteral lipids.

The relationship between comorbidities of prematurity and the occurrence of EUGR for weight, length, and HC is presented in Table 6. With the cross-sectional definition, SGA infants developed EUGR more frequently for all three anthropometric parameters. In contrast, they developed EUGR less frequently for weight and HC per the longitudinal definitions. According to these findings, SGA infants showed significantly higher Δ*Z*-scores for weight and HC (see Supplementary Material). Late–onset sepsis was significantly associated with EUGR for weight according to the longitudinal definition. Other evaluated comorbidities (EOS, IVH, NEC, PDA, BPD, and ROP) were not associated with EUGR. Infants who developed LOS showed significantly lower Δ*Z*-scores of lengths (Supplementary Material). Similarly, infants with NEC showed a significantly lower Δ*Z*-scores for lengths and HC (see Supplementary Material).

The complications related to PN showed associations with the demographic characteristics of the patients at birth, the duration of PN, and the parenterally administered nutrients (Table 7). Cholestasis was significantly associated with lower birth weight,

Table 2: Comparison between cross-sectional (below 10th percentile) and longitudinal (*Z*-score loss > 1) EUGR definitions among different sizes, and comparison of demographic characteristics between infants with or without EUGR for different definitions of the three anthropometric parameters

	EUGR–weight (below 10th percentile)			
	No, n = 66 (55)		*Yes, n = 53 (45)****	
Gestational age (weeks)	28.8***	(27.5–30.5)	31.5***	(29.0–32.7)
Birth weight (gm)	1145	(948–1339)	1043	(905–1305)
Birth length (cm)	38.0	(35.0–39.0)	36.7	(34.5–40.0)
Birth head circumference (cm)	26.2	(25.0–27.5)	26.0	(24.7–28.0)
	EUGR–weight (Z-score loss > 1); no (0) yes (1)			
	No, n = 95 (80)		*Yes, n = 24 (20)****	
Gestational age (weeks)	30.50***	(28.0–32.0)	28.43***	(26.8–29.1)
Birth weight (gm)	1137	(932–1335)	1040	(667–1329)
Birth length (cm)	37.5	(35.0–40.0)	37.0	(34.6–39.0)
Birth head circumference (cm)	26.5	(25.0–28.0)	25.0	(23.1–27.0)
	EUGR–length (below 10th percentile); no (0) yes (1)			
	No, n = 51 (43)		*Yes, n = 68 (57)*	
Gestational age (weeks)	29.7	(28.0–30.8)	29.7	(27.5–32.3)
Birth weight (gm)	1221**	(998–1380)	997**	(734–1270)
Birth lengths (cm)	38.5**	(37.0–40.0)	36.0**	(34.5–38.5)
Birth head circumference (cm)	26.5	(25.0–28.0)	26.0	(24.0–27.6)

(Contd)

Table 2: *(Contd...)*

	EUGR–length (Z-score loss > 1); no (0) yes (1)			
	No, n = 65 (55)		*Yes, n = 54 (45)*	
Gestational age (weeks)	30.6**	(28.8–31.9)	28.43**	(27.2–31.2)
Birth weight (gm)	1215**	(977–361)	996**	(707–1225)
Birth length (cm)	38.0	(35.0–39.0)	36.7	(35.0–9.7)
Birth head circumference (cm)	27.0*	(25.1–28.0)	25.5*	(23.6–27.0)
	EUGR–HC (below 10th percentile); no (0) yes (1)			
	No, n = 75 (63)		*Yes, n = 44 (37)***	
Gestational age (weeks)	29.9	(28.0–31.6)	29.0	(27.5–32.5)
Birth weight (gm)	1200**	(972–1366)	991.0*	(669–1211)
Birth length (cm)	38.0***	(36.0–40.0)	35.7***	(33.0–38.0)
Birth head circumference (cm)	27.0**	(25.0–28.0)	25.5**	(22.5–27.0)
	EUGR–HC (Z-score loss > 1); no (0) yes (1)			
	No, n = 97 (81.5)		*Yes, n = 22 (18.5)***	
Gestational age (weeks)	30.0**	(28.0–31.8)	28.1**	(26.0–29.6)
Birth weight (gm)	1171*	(948–1340)	978*	(721–1187)
Birth length (cm)	37.7	(35.0–40.0)	36.0	(34.7–38.2)
Birth head circumference (cm)	26.0	(25.0–28.0)	26.2	(23.2–27.0)

Values are expressed as number (%) and median (IQ). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ by Fisher's exact test or Mann–Whitney *U* test.

Table 3: Comparison of nutrition between infants with or without EUGR for weight according to cross-sectional (below 10th percentile) and longitudinal (*Z*-score loss > 1) definitions

	EUGR–weight (below 10th percentile)			
	No, n = 64		*Yes, n = 46*	
Duration of PN (days)	17	(12–25)	15	(11–29)
First day of MEF	1	(1–2)	2	(1–2)
First day of FEF	27	(18–37)	23	17–39
PN kcal	73.0	(69.6–77.5)	74.7	(69.2–79.4)
Total kcal	103.7	(99.2–108.2)	102.0	98.2–108.8
PN carbohydrate (gm)	10.2	9.6–11.1	10.7	9.5–11.4
Total carbohydrate (gm)	13.3	12.8–14.0	13.5	12.7–14.3
PN protein (gm)	3.1	2.9–3.2	3.1	3–3.2
Total protein (gm)	3.7	3.6–3.8	3.7	3.6–3.8
PN lipid (gm)	2.2	1.8–2.4	2.0	1.8–2.3
Total lipid (gm)	3.5	3.3–3.9	3.6	3.2–3.9
PN calcium 7 days (mg)	62.8	57.8–68.5	62.8	57.6–68.5
PN phosphorus 7 days (mg)	49.8	45.7–55.0	51.4	47.8–55.7
Ca/P ratio 7 days	0.98*	(0.94–1.02)	0.95*	(0.91–0.98)
	EUGR–weight (Z-score loss > 1)			
	No, n = 88		*Yes, n = 20*	
Duration of PN (days)	14.5*	(11.0–22.0)	25.0*	(19.2–43.7)
First day of MEF	1.0	(1.0–2.0)	1.0	(1.0–2.0)
First day of FEF	23.0*	(17.0–30.0)	38.5*	(27.0–49.5)
PN kcal	74.5	(69.6–78.0)	71.2	(67.6–80.2)
Total kcal	102.5	(98.5–108.1)	105.1	(100.9–109.2)
PN carbohydrates (gm)	10.4	(9.6–11.2)	10.4	(9.2–11.5)
Total carbohydrates (gm)	13.3	(12.7–14.0)	13.4	(13.0–14.3)
PN protein (gm)	3.1	(2.9–3.2)	3.1	(2.9–3.2)
Total protein (gm)	3.7	(3.5–3.8)	3.7	(3.7–3.8)
PN lipid (gm)	2.2	(1.9–2.3)	2.0	(1.8–2.4)

Total lipid (gm)	3.5	(3.2–3.9)	3.8	(3.4–4.1)
PN calcium 7 days (mg)	62.8	(58.6–68.6)	62.8	(56.4–68.4)
PN phosphorus 7 days (mg)	50.8	(46.4–55.7)	50.0	(45.9–54.4)
Ca/P ratio 7 days	0.97	(0.94–1.01)	0.95	(0.9–1.0)

Values are expressed as median (IQ); *$p < 0.01$ by Mann–Whitney *U* test. FEF, full enteral feeding; MEF, minimal enteral feeding

Table 4: Comparison of nutrition between infants with or without EUGR for length according to cross-sectional (below 10th percentile) and longitudinal (*Z*-score loss > 1) definitions.

	EUGR–length (below 10th percentile)			
	No, n = 48		*Yes, n = 62*	
Duration of PN (days)	16	(11–22)	18	(12–35)
First day of MEF	1	(1–2)	2	(1–2)
First day of FEF	26	(17–30)	25	(19–45)
PN kcal	75.0	(69.6–78.7)	73.4	(68.9–78.2)
Total kcal	104.1	(99.8–108.8)	102.9	(98.7–108.2)
PN carbohydrate (gm)	10.3	(9.6–11.1)	10.5	(9.5–11.3)
Total carbohydrate (gm)	13.3	(12.6–14.0)	13.4	(12.9–14.2)
PN protein (gm)	3.1	(2.9–3.2)	3.1	(2.9–3.2)
Total protein (gm)	3.7	(3.6–3.8)	3.7	(3.6–3.8)
PN lipid (gm)	2.2**	(1.9–2.4)	2.0**	(1.7–2.2)
Total lipid (gm)	3.7	(3.4–3.9)	3.5	(3.2–3.9)
PN calcium 7 days (mg)	61.4	(57.1–69.3)	63.6	(58.6–68.6)
PN phosphorus 7 days (mg)	49.3	(45.7–55.7)	51.2	(48.0–55.3)
Ca/P ratio 7 days	0.97*	(0.94–1.02)	0.96*	(0.91–1.00)
	EUGR–length (Z-score loss > 1)			
	No, n = 61		*Yes, n = 69*	
Duration of PN (days)	14.0*	(11.0–23.0)	19.0*	(13.0–36.5)
First day of MEF	1.0	(1.0–2.0)	2.0	(1.0–2.0)
First day of FEF	22.0**	(17.0–30.0)	29.0**	(19.0–49.0)
PN kcal	73.4	(70.3–78.0)	73.5	(67.1–78.2)
Total kcal	102.7	(99.3–107.8)	103.4	(98.5–108.8)
PN carbohydrate (gm)	10.4	(9.6–11.1)	10.3	(9.5–11.3)
Total carbohydrate (gm)	13.4	(12.724–14.0)	13.4	(12.9–14.3)
PN protein (gm)	3.1	(2.9–3.2)	3.1	(3.0–3.2)
Total proein (gm)	3.7	(3.6–3.8)	3.7	(3.6–3.8)
PN lipid (gm)	2.2**	(1.9–2.4)	2.0**	(1.7–2.2)
Total lipid (gm)	3.6	(3.3–3.9)	3.5	(3.3–4.0)
PN calcium 7 days (mg)	62.1	(57.3–69.1)	63.9	(57.8–68.2)
PN phosphorus 7 days (mg)	50.0	(45.7–55.9)	50.7	(47.8–54.7)
Ca/P ratio 7 days	0.97	(0.94–1.0)	0.95	(0.92–1.0)

Values are expressed as median (IQ); *$p < 0.05$; **$p < 0.01$ by Mann–Whitney *U* test. FEF, full enteral feeding; MEF, minimal enteral feeding

but not with PN intakes. Hyperglycemia requiring insulin treatment was seen more frequently in infants with lower gestational age and lower birth weight, but not with carbohydrate intakes. The occurrence of hypertriglyceridemia was associated with lower gestational age and birth weight, but not with the total lipid intake. Cholestasis, hyperglycemia requiring insulin treatment, and hypertriglyceridemia were significantly associated with longer PN duration. Logistic regression confirmed these associations, but with a very low magnitude (see Supplementary Material). We did not find an association between calcium and phosphorus metabolism

Table 5: Comparison of nutrition between infants with or without EUGR for HC according to cross-sectional (below 10th percentile) and longitudinal (*Z*-score loss > 1) definitions

	EUGR–HC (below 10th percentile)			
	No, n = 71		*Yes, n = 39*	
Duration of PN (days)	16	(12–20)	19	(11–36)
First day of MEF	1	(1–2)	2	(1–2)
First day of FEF	24	(17–34)	28	(17–45)
PN kcal	75.4	(69.6–79.1)	72.5	(68.3–76.8)
Total kcal	103.8	(99.8–108.5)	101.7	(98.2–108.0)
PN carbohydrate (gm)	10.5	(9.6–11.2)	10.4	(9.4–11.3)
Total carbohydrate (gm)	13.4	(12.8–14.0)	13.4	(12.5–14.2)
PN protein (gm)	3.1	(2.9–3.2)	3.1	(2.9–3.2)
Total protein (gm)	3.7	(3.6–3.8)	3.7	(3.6–3.8)
PN lipid (gm)	2.2*	(1.9–2.3)	2.0*	(1.7–2.2)
Total lipid (gm)	3.6	(3.3–3.9)	3.6	(3.2–3.8)
PN calcium 7 days (mg)	63.5	(57.8–70.7)	62.5	(56.4–67.5)
PN phosphorus 7 days (mg)	51.3	(45.7–56.4)	50.5	(46.9–54.7)
Ca/P ratio 7 days	0.97	(0.93–1.0)	0.95	(0.91–0.99)
	EUGR–HC (Z-score loss >1)			
	No, n = 93		*Yes, n = 17*	
Duration of PN (days)	16	(12–26)	19	(13–33)
First day of MEF	1	(1–2)	2	(1–2)
First day of FEF	24	(17–38)	30	(19–38)
PN kcal	74.2	(69.5–78)	71.4	(68.7–76.1)
Total kcal	103.6	(98.9–108.6)	102.9	(97.6–105.6)
PN carbohydrate (gm)	10.4	(9.6–11.2)	10.2	(9.5–11.4)
Total carbohydrate (gm)	13.4	(12.7–14.2)	13.4	(12.9–13.9)
PN protein (gm)	3.1	(2.9–3.2)	3.1	(3.0–3.2)
Total protein (gm)	3.7	(3.6–3.8)	3.7	(3.6–3.8)
PN lipid (gm)	2.2*	(1.9–2.4)	2.0*	(1.6–2.2)
Total lipid (gm)	3.6	(3.3–3.9)	3.4	(2.9–3.8)
PN calcium 7 days (mg)	62.8	(57.8–68.5)	63.6	(57.5–67.8)
PN phosphorus 7 days (mg)	50.9	(45.9–55.7)	49.6	(46.6–52.6)
Ca/P ratio 7 days	0.96	(0.93–1.0)	1.0	(0.94–1.0)

Values are expressed as median (IQ); *$p < 0.05$ by Mann–Whitney *U* test. FEF, full enteral feeding; MEF, minimal enteral feeding

disorders with gestational age, birth weight, parenteral calcium and phosphorus intakes, and Ca/P ratio at 7 days of life.[48] Being SGA was also not associated with metabolism disorders of calcium and phosphate (Table 8).

Based on logistic regression, infants who developed EUGR for weight according to the cross-sectional definition were more significantly SGA at birth [logit: 3.7; OR: 42.5 (95% CI: 12.4–142.1); $p < 0.001$)]. Other demographic characteristics at birth, the length of PN dependence, and the occurrence of both LOS and NEC were not different from those who did not have EUGR for weight. Appling the longitudinal definition of EUGR for weight, no differences were observed using logistic regression analysis.

Infants with EUGR for length, according to cross-sectional definition, showed significantly lower gestational age, birth weight, and parenteral lipid intake compared to those who did not develop EUGR [logit -1.8; OR 0.16 (95% CI 0.04–0.68); $p = 0.013$]. The demographic characteristics at birth, duration of PN, and the occurrence of SGA, LOS, and NEC were similar between the same two groups. Similarly, applying the longitudinal definition of EUGR for length, infants with EUGR received lower parenteral lipid intakes [logit: –1.4; OR: 0.25 (95% CI: 0.07–0.85); $p = 0.026$] and had lower birth length; no other differences were observed using logistic regression analysis.

Logistic regression showed that infants who had EUGR for HC according to the cross-sectional definition, were more frequently SGA [logit: –1.5; OR: 4.6 (95% CI: 1.82–11.48); $p = 0.001$], whereas the other demographic characteristics at birth, the number of PN days, the parenteral lipid intake and the occurrence of both LOS and NEC were similar to infants who did not have EUGR for HC. When the longitudinal definition was used for EUGR for HC, infants with EUGR had lower parenteral lipid intakes [logit: –1.45; OR: 0.23 (95% CI: 0.06–0.91); $p = 0.037$]. No other differences were noted in logistic regression.

Discussion

We present an observational study of 119 preterm VLBW infants who were treated with PN using a specifically designed web-based

Table 6: Comparison between comorbidities of prematurity and EUGR occurrence

	SGA		*EOS*		*LOS*		*NEC*		*BPD*		*IVH*		*ROP*		*PDA*	
	No (N = 77)	*Yes (N = 42)*	*No (N = 115)*	*Yes (N = 4)*	*No (N = 95)*	*Yes (N = 24)*	*No (N = 117)*	*Yes (N = 2)*	*No (N = 77)*	*Yes (N = 42)*	*No (N = 113)*	*Yes (N = 6)*	*No (N = 115)*	*Yes (N = 4)*	*No (N = 95)*	*Yes (N = 24)*
EUGR–weight < 10th percentile	16*** (20)	37888 (88)	52 (45.2)	1 (25)	45 (47.3)	8 (33.3)	52 (45.2)	1 (50)	38 (49.3)	15 (35.7)	51 (45.1)	2 (33.3)	52 (45.2)	1 (25)	43 (45.2)	10 (41.6)
EUGR–weight loss *Z* > 1	20** (26)	3** (7)	21 (18.2)	2 (50)	16 (16.8)	7 (29.1)	22 (18.8)	1 (50)	14 (18.1)	9 (21.4)	21 (18.5)	2 (33.3)	23 (20)	0	17 (17.8)	6 (25)
EUGR–length < 10th percentile	36** (46)	32** (76)	66 (57.3)	2 (50)	5 (57.8)	13 (54.1)	67 (57.2)	1 (50)	42 (54.5)	26 (61.9)	65 (57.5)	3 (50)	66 (57.3)	2 (50)	54 (56.8)	14 (58.3)
EUGR–length loss *Z* > 1	36 (46)	16 (38)	51 (44.3)	1 (25)	36* (37.8)	16* (66.6)	51 (43.5)	1 (50)	30 (38.9)	22 (52.3)	50 (44.2)	2 (33.3)	51 (44.3)	1 (25)	39 (41)	13 (54.1)
EUGR–HC < 10th percentile	22** (28)	22** (52)	42 (36.5)	2 (50)	34 (35.7)	10 (41.6)	43 (36.7)	1 (50)	29 (37.6)	15 (35.7)	42 (37.1)	2 (33.3)	42 (36.5)	2 (50)	35 (36.8)	9 (37.5)
EUGR–HC loss *Z* > 1	18* (23)	2* (5)	18 (15.6)	2 (50)	15 (15.7)	5 (20.8)	19 (16.2)	1 (50)	12 (15.5)	8 (19)	20 (17.6)	0	0	0	15 (15.7)	5 (20.8)

Values are expressed as number (%). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ by Fisher's exact test. BPD, bronchopulmonary dysplasia; EOS, early onset sepsis; IVH, intraventricular hemorrhage; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus, ROP, retinopathy of prematurity; SGA, small for gestational age

electronic prescription system. As shown in Table 3, all nutritional intakes, including that of carbohydrates, amino acids, lipids, calcium, and phosphorus, were consistent with the currently available guidelines.[24,25] Comparing nutritional intakes, we found that infants with EUGR for length and HC had received lower parenteral lipid intake than the non-EUGR infants (see Tables 4 and 5). These findings can be explained by considering that infants with EUGR for length and HC had significantly lower birth weights and may have had lower parenteral lipid tolerance. In addition, multivariate analysis controlling for the effect of other risk factors, such as prematurity and birth weight, showed a significant association between parenteral lipid intake and occurrence of cross-sectional EUGR for length and longitudinal EUGR for length and HC. These results suggest that lower parenteral lipid intake may be an independent risk factor for inferior growth outcomes for weight and HC in preterm VLBW infants.

In our study, among the comorbidities of prematurity, LOS was most frequently associated with longitudinal EUGR for length (Table 6). However, multivariate analysis did not confirm this association (see Supplementary Material). SGA infants were significantly more prone to be classified as EUGR when the cross-sectional definition was used. Interestingly, the longitudinal definition showed lower frequencies of EUGR than the cross-sectional definition. These findings could be explained by considering that the two different definitions of EUGR are based on arbitrary cut-off values that differ from each other. Our study showed that the incidence of EUGR was significantly different depending on the adopted definition (see Table 2).

SGA infants, who had poor intrauterine growth,[49] had a higher probability of having EUGR per the cross-sectional definition with a discharge weight <10th percentile for gestational age. In contrast, these infants were at lower risk of poor postnatal growth and EUGR per the longitudinal definition. These findings were confirmed in logistic regression; in our cohort, cross-sectional EUGR for weight and HC were associated with lower birth weights than longitudinal EUGR (see Supplementary Material). The results of this study suggest that the longitudinal EUGR definition using the INTERGROWTH-21st standards could be more appropriate to identify the risk of postnatal growth failure in preterm VLBW infants.[50] However, these findings need confirmation; one important limitation of our study is that there were only a few preterm births with the lowest gestational ages in our cohort.[24] The construction of standard charts for extremely preterm infants is problematic because there is no definitive information on the nutritional requirements of this relatively-limited population.[51] During the first postnatal weeks, monitoring of growth should be performed only to trace a growth trajectory rather than used as a tool to identify EUGR.

Regarding the safety of PN, it is already known that electronic prescribing systems can decrease the risk of errors and the use of a standardized electronic tool for PN prescription is recommended.[11,52] In our study, the use of Par/Ent®, a specifically-designed web-based system for neonatal care, allowed us to identify any association(s) between the nutritional intakes and the complications secondary to PN administration (Tables 7 and 8). No significant associations were found for cholestasis, hyperglycemia with the need for insulin treatment, hypertriglyceridemia, and disorders of calcium/phosphorus homeostasis. However, once again, the number of infants observed in our cohort might not be sufficient to rule out such associations.[53] Similarly, the absence of associations between EUGR and the most of comorbidities of prematurity might depend on the limited number of observations.[54]

Table 7: Relationship between PN complications, demographic characteristics at birth, duration of PN or parenteral nutrients intake

	Cholestasis			
	No, n = 96		*Yes, n = 23*	
Gestational age (weeks)	29.9	(28.0–31.9)	29.0	(27.8–30.7)
Birth weight (gm)	1165*	(940–1343)	982*	(695–1173)
Duration of PN (days)	14.5***	(11.0–21.0)	32.5***	(19.0–49.0)
PN kcal	73.6	(69.4–78.3)	73.6	(69.6–80.9)
PN carbohydrate (gm)	10.3	(9.5–11.1)	11.0	(9.9–11.5)
PN protein (gm)	3.1	(2.9–3.2)	3.0	(2.9–3.2)
PN lipid (gm)	2.2	(1.9–2.3)	2.0	(1.8–2.3)
SGA	33	(34)	9	(39)
	Insulin treatment for hyperglycemia			
	No, n = 108		*Yes, n = 11*	
Gestational age (weeks)	30.0***	(28.0–31.9)	24.8***	(24.5–28.3)
Birth weight (gm)	1171.5***	(967–1339.5)	658***	(577.2–706.2)
Duration of PN (days)	16**	(11–23)	46**	(23–53)
PN kcal	74.6	(69.4–78.6)	70.988	(69.8–71.9)
PN carbohydrate (gm)	10.4	(9.6–11.2)	10.229	(9.6–10.8)
SGA	38	(35)	4	(36)
	Hypertriglyceridemia			
	No, n = 91		*Yes, n = 27*	
Gestational age (weeks)	30.3***	(28.4–32.0)	26.6***	(24.7–29.0)
Birth weight (gm)	1180***	(987–1345.2)	695***	(593–1023.2)
Duration of PN (days)	15***	(11–20)	36***	(19–47)
PN kcal	75.0	(69.5–79.0)	72.0	(69.8–77.3)
PN lipid (gm)	2.2	(1.9–2.4)	2.0	(1.5–2.3)
SGA	33	(36)	9	(33)

Values are expressed as number (%) and median (IQ); *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ by Fisher's exact test or Mann–Whitney U test.

Table 8: Relationship between metabolism disorders of calcium and phosphorus, demographic characteristics at birth and parenteral intakes of calcium and phosphorus.

	Hypophosphatemia 7 days			
	No, n = 61		*Yes, n = 58*	
Gestational age (weeks)	29.2	(27.8–31.3)	30.1	(28–32)
Birth weight (gm)	1187.5	(965.5–1339.5)	998	(920–1302)
PN calcium 7 days (mg)	62.5	(56.6–68.6)	64.3	(58.6–69.3)
PN phosphorus 7 days (mg)	49.6	(45.7–55.0)	52.1	(48.6–57.1)
Ca/P ratio 7 days	0.97	(0.94–1.0)	0.95	(0.93–1.0)
SGA	16	(26.2)	26	(44.8)
	Hypophosphatemia > 7 days			
	No, n = 101		*Yes, n = 18*	
Gestational age (weeks)	30	(28–32)	28	(25.4–29.6)
Birth weight (gm)	1165	(967–1339.5)	781	(658–1100)
PN calcium 7 days (mg)	62.8	(57.8–68.5)	63.2	(59–68.6)
PN phosphorus 7 days (mg)	50.7	(46.2–55.3)	51.1	(48.6–55.7)
Ca/P ratio 7 days	0.97	(0.93–1.0)	0.9	(0.91–1.0)
SGA	36	(35.6)	6	(33.3)
	Severe hypophosphatemia 7 days			
	No, n = 110		*Yes, n = 9*	
Gestational age (weeks)	29.7	(27.9–31.8)	28.4	(27.9–30.9)
Birth weight (gm)	1140	(931–1338)	943	(631.7–979)
PN calcium 7 days (mg)	62.8	(57.8–68.5)	64.3	(62.3–67.7)
PN phosphorus 7 days (mg)	50.3	(45.9–55)	56.4	(52.3–61.2)

Ca/P ratio 7 days	0.97	(0.93–1.0)	0.90	(0.87–0.95)
SGA	36	(32.7)	6	(66.6)
	Hypercalcemia			
	No, n = 106		*Yes, n = 13*	
Gestational age (weeks)	30	(28–31)	27.8	(24.8–29.0)
Birth weight (gm)	1135	(946.7–1320)	780.000	(637–1339)
PN calcium 7 days (mg)	62.8	(57.8–68.6)	66.429	(61.1–69.3)
PN phosphorus 7 days (mg)	50.7	(46.3–55.0)	55.000	(49.2–56.6)
Ca/P ratio 7 days	0.97	(0.93–1.0)	0.966	(0.93–1.0)
SGA	39	(36.7)	3	(23.1)

Values are expressed as number (%) and median (IQ); No difference by Fisher's exact test or by Mann–Whitney U test.

Conclusion

Even with the declared limitations, this study has highlighted the possible benefits of using a computerized web-based system for prescribing PN in the NICU setting. Our experience could be useful in designing a larger project to be applied within a neonatal network to evaluate the effects of PN on postnatal growth.

Clinical Significance

The use of a web-based system for the electronic prescribing of PN in neonatal care could help neonatologists in ensuring the correct intake of nutrients in preterm VLBW infants.

Author Contributions

Mario Motta and Salvatore Aversa contributed equally to the manuscript. All authors contributed to the manuscript revision, review, and approved the submitted version.

Supplementary Material

The supplementary material is available online on the website of https://www.newbornjournal.org/

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