Characteristics and risk factors for extrauterine growth retardation in very-low-birth-weight infants

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Abstract

This study aimed to investigate the characteristics and risk factors for extrauterine growth retardation (EUGR) in very-low-birth-weight infants (VLBWIs). The medical records of 137 VLBWIs admitted to the neonatal intensive care unit between June 2015 and December 2017 were retrospectively reviewed. The patients were divided into EUGR (n = 92) and non-EUGR (n = 45) groups. The data of demographic and clinical characteristics was collected and the risk factors for EUGR were assessed by multivariate logistic regression analysis. Gestational age (OR = 0.573, P < 0.01), SGA (OR = 3.887, P = 0.022), feeding intolerance (OR = 4.632, P = 0.002), and calories supplied by amino acids at the 7 th day (OR = 0.786, P = 0.006) were independent high-risk factors for EUGR. EUGR in VLBWIs may be prevented by strategies including early lactation, providing special formulas to reduce feeding intolerance, and sufficient calorie provision.This study aimed to investigate the characteristics and risk factors for extrauterine growth retardation (EUGR) in very-low-birth-weight infants (VLBWIs). The medical records of 137 VLBWIs admitted to the neonatal intensive care unit between June 2015 and December 2017 were retrospectively reviewed. The patients were divided into EUGR (n = 92) and non-EUGR (n = 45) groups. The data of demographic and clinical characteristics was collected and the risk factors for EUGR were assessed by multivariate logistic regression analysis. Gestational age (OR = 0.573, P < 0.01), SGA (OR = 3.887, P = 0.022), feeding intolerance (OR = 4.632, P = 0.002), and calories supplied by amino acids at the 7 th day (OR = 0.786, P = 0.006) were independent high-risk factors for EUGR. EUGR in VLBWIs may be prevented by strategies including early lactation, providing special formulas to reduce feeding intolerance, and sufficient calorie provision.

Introduction

The survival of very-low-birth-weight infants (VLBWIs) has improved with the development of technologies on perinatal care, neonatal intensive care, respiratory support, and nutrition support [1, 2]. However, weight gain in VLBWIs is usually difficult to achieve due to delayed maturation of various organs and underlying diseases. Extrauterine growth retardation (EUGR) is commonly seen in preterm infants [3]. The incidence of EUGR in VLBWIs is strikingly high, reaching 43–97% [4–6].

EUGR in VLBWIs is an important issue in the clinic. EUGR is defined as growth parameters, usually body weight, height, and head circumference, below the 10^{th} percentile of premature infants at discharge [3]. Based on the nutrition program theory, EUGR has an irreversible long-term effect on neurodevelopment and adult body height [7, 8]. However, evidence has demonstrated that an early aggressive nutrition plan can reduce the incidence of EUGR in VLBWIs [9, 10]. In this retrospective study, we sought to evaluate the characteristics and risk factors for EUGR in VLBWIs in order to determine the optimal postnatal nutrition mode so that growth retardation can be prevented.

Methods

Patients and study design

The medical records of VLBWIs admitted to the neonatal intensive care unit at the Children's Hospital of Soochow University between June 2015 and December 2017 were retrospectively reviewed. The inclusion criteria were as follows: 1) gestational age ≤ 32 weeks, 2) admitted within postnatal 24 h, 3) duration of hospital stay ≥ 28 days, 4) vital signs were stable at discharge; no bruising, no apnea, oral feeding completely; 5) with complete medical records. The exclusion criteria included the following: 1) having an underlying disease such as a congenital genetic metabolic disease, severe congenital heart disease, or gastrointestinal malformation; 2) hospital duration ≤ 4 weeks; 3) poor milk consumption at discharge; 4) unstable vital signs at admission.

Demographic and clinical parameters

Characteristics including gender, gestational age, birth weight, age at admission, and small for gestational age (SGA) were collected. The occurrence of neonatal respiratory distress syndrome (NRDS), neonatal pneumonia, or asphyxia was recorded. The following parameters were compared between groups: hospital stay, duration of intravenous nutrition support, initiation time of lactation, feeding intolerance rate, time of minimum weight, weight loss, time of return to birth weight, initiation time of amino acid application, initiation time of oral fat emulsion, age of oral calorie intake reaching 120 kcal/kg/d, fluid intake at the 3rd and 7^{th} days, total calories supplied intravenously, calories supplied by intravenous amino acids, calories provided by intravenous fat emulsion, and weight changes.

Records including nutritional intake, weight gain, underlying diseases, complications, length of hospital stay, and physical development at discharge were collected. Informed consent was obtained from a guardian of each patient. The study was approved by the Ethics Committee of the Children's Hospital of Soochow University, and all research were performed in accordance with relevant guidelines and regulations.

Evaluation criteria

The following formulas were used:

Postnatal weight loss (%) = (birth weight - minimum weight) / birth weight × 100%,

Weight gain rate (g/kg/d) = (body weight at discharge - birth weight) / (length of hospital stay × birth weight).

Statistical analysis

Data were analyzed using IBM SPSS statistics software version 17.0. Data were expressed as the mean ± standard deviation for normally distributed variables, or as the median (P25, P75) for non-normally distributed data. The T-test and the Z-test were performed to determine the differences between groups. Differences in clinicopathological features among groups were tested using Pearson's chi-squared (χ^2) test or Fisher's exact test for categorical variables. Logistic regression analysis was applied to evaluate the risk factors for EUGR. The variables with statistical significance ($P < 0.1$) by univariate analysis were included in a multivariate analysis. All reported P values were two-tailed. A P value < 0.05 was considered as statistically significant.

Results

Demographic and clinical characteristics

Among the 137 VLBWIs included in this study, there were 62 males and 75 females. The number of SGA infants was 30 (21.9%). All patients received total parenteral nutrition through an intravenous line. A total of 92 (67.2%) infants had EUGR at discharge. In the EUGR group, there were 42 males and 50 females. The patient characteristics, including gender, age at admission, and the incidence of NRDS, neonatal pneumonia, and asphyxia, were not significantly different between groups. The gestational age of the EUGR group and the non-EUGR group ranged from 26 weeks^{+3} to 32 weeks and 25 weeks^{+6} to 32 weeks, respectively. The average gestational age of the non-EUGR group was significantly greater than that of the EUGR group (30.50 ± 1.41 weeks vs. 29.67 ± 1.44 weeks, P = 0.002). Similarly, the birth weight of the non-EUGR group was substantially greater than that of the EUGR group (1294.78 ± 170.15 g vs. 1206.90 ± 182.30 g, P = 0.008). The number of patients with SGA in the EUGR group was significantly greater than that of the non-EUGR group [25 (27.5%) vs. 5 (11.1%), P = 0.030] (Table 1).

The length of hospital stay and the duration of intravenous nutrition were significantly longer in the EUGR group compared to the non-EUGR group (P < 0.05). The initiation time of lactation was earlier in the non-EUGR group than in the EUGR group (P = 0.017). The incidence of feeding intolerance was significantly higher in the EUGR group compared with the non-EUGR group (P = 0.002). However, characteristics including age of minimum weight, weight loss, age of birth weight recovery, initiation time of amino acid application, initiation time of oral fat emulsion, and time of oral calorie intake reaching 120 kcal/kg/d were not significantly different between the groups (Table 1).

Comparison of complications between the EUGR and non-EUGR groups

The incidence of complications, including hyperbilirubinemia, septicemia, anemia, intracranial bleeding, periventricular leukomalacia, hypoxic ischemic encephalopathy, intracranial infection, pulmonary hemorrhage, neonatal hypoglycemia, liver dysfunction, necrotizing enterocolitis (NEC), and patent ductus arteriosus (PDA), was compared between the EUGR and non-EUGR groups. There were no significant differences in these complications between the groups (all P > 0.05). However, a marginal trend toward significance was noted in the occurrence of neonatal hypoglycemia (P = 0.063) (Table 1).

Nutritional status and changes of body weight during the hospital stay

Comparing the nutritional status and body weight changes, on both the 3rd and the 7th day, there were no significant differences in the total fluid intake or calories supplied by intravenous nutritional therapy or fat emulsion between the EUGR and the non-EUGR groups (all P > 0.05). The calories supplied by amino acids at the 7th day were significantly greater in the non-EUGR group than in the EUGR group (P = 0.007). Although the total calorie intake was not significantly different between the groups within the first 14 days (all P > 0.05), a significantly greater total calorie intake was observed on the 28th day in the non-EUGR group compared with the EUGR group (P = 0.049). For the changes of body weight, infants in the non-EUGR group showed a persistently greater body weight compared with those in the EUGR group (all P < 0.05, except a marginal trend toward significance at the 14th day) (Tables 2–3).

Independent risk factors for EUGR

All parameters were included in the multivariate logistic analysis to evaluate the risk factors for EUGR. The analysis demonstrated that four factors: gestational age (OR = 0.573, P = 0.001), SGA (OR = 3.887, P = 0.022), feeding intolerance (OR = 4.632, P = 0.002), and calories supplied by amino acids at the 7th day (OR = 0.786, P = 0.006) were associated with EUGR (Table 4).

Discussion

The current study investigated the nutritional status and risk factors for EUGR in VLBWIs. Our findings revealed that characteristics including gestational age, birth weight, proportion of SGA infants, length of hospital stay, feeding intolerance percentage, initiation time of lactation, duration of intravenous nutrition, calories supplied by amino acids at the 3rd day, total calorie intake at the 28th day, and body weight at the 3rd, 7th, 28th day, and at discharge were significantly different between the EUGR and non-EUGR groups. More importantly, gestational age, SGA, feeding intolerance, and calories supplied by amino acids at the 7th day were high risk factors for EUGR.

EUGR is a serious clinical problem that occurs frequently in VLBWIs [3, 11]. Although only 27.5% of VLBWIs included in the present study were SGA at birth, 67.2% eventually developed EUGR. The incidence of EUGR in the current study was in line with previous studies [6, 12]. Growth failure in VLBWIs may result from multiple factors such as difficulties in digestion, endocrine abnormalities, central nervous system impairment, and morbidities affecting nutrient requirements [13]. Insufficient nutrition, especially within the first postnatal weeks, is largely responsible for the occurrence of EUGR [14].

Our findings confirmed the fact that gestational age is an independent risk factor for EUGR [11, 15]. It is reasonable that the more mature the infant was, the better the development of organ function and the reduced possibility of feeding intolerance and underlying diseases. Of note, EUGR can be assessed by the body weight, head circumference, and body length of the infant. A limitation of this study is that the body weight was the only criterion used for EUGR.

Early feeding and nutritional support are strategies for the prevention of EUGR [4, 9, 16]. Early enteral feeding improves the gastrointestinal tolerance and boosts the growth of the digestive tract [9]. For VLBWIs to achieve the required amounts of nutrition, parenteral feeding is necessary in addition to enteral feeding [17, 18]. In this study, the infants in both the EUGR and non-EUGR groups received intravenous nutritional support before the start of enteral nutrition. For the start time of enteral feeding, an early initiation within the first three days after birth is suggested [19]. The time of initiation of oral feeding was later in the EUGR group compared with that in the non-EUGR group. In addition, feeding intolerance due to a delayed enteral feeding had a negative effect on the body weight gain. Not surprisingly, our results revealed that feeding intolerance was a risk factor for EUGR.

Early enteral feeding decreases the risk of NEC. However, the incidence of complications including NEC did not differ between the groups in the current study, which was not consistent with findings from previous studies [16]. The limited sample size and observation period in our study may partly explain this discrepancy.

A prompt provision of amino acids induces body weight gain and prevents the occurrence of EUGR in VLBWIs [20]. We found that calories supplied by intravenous amino acids at the 7th day had a positive effect on body weight gain. The body weight in the non-EUGR group was greater than that in the EUGR group, along with higher calories provided by intravenous amino acids. A local multicenter study pointed out that aggressive nutritional management decreased the incidence of EUGR in VLBWIs [11]. The updated 2013 version of the Chinese guidelines for nutrition support in neonates recommend a daily calorie intake of 120 kcal/kf/d. Specifically, the total calorie intake is recommended to be 105–130 kcal/kg/d for neonates, 110–135 kcal/kg/d for premature infants, and up to 150 kcal/kg/d for VLBWIs. Within the first postnatal week, a remarkably lower body weight was noticed in the EUGR group. However, this difference between the EUGR and non-EUGR groups disappeared at the 14th day, indicating a positive effect of early nutrition support on body weight. With the increase in calorie requirements due to metabolic abnormalities or disease, however, the total calorie intake in the EUGR group decreased, which resulted in a lower body weight compared to the non-EUGR group.

The nutrition support guidelines currently implemented are based on the intrauterine growth indicators of normal fetuses. They do not accurately reflect the pathophysiological status of premature infants. Clinically, individualized nutrition support strategies should be applied for VLBWIs in order to reduce the incidence of EUGR and to improve the long-term prognosis.

In conclusion, strategies such as early initiation of oral feeding, use of special formulas to reduce feeding intolerance, and amino acid nutrition support should be applied to prevent delayed extrauterine growth for VLBWIs.

Declarations

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical approval: The study was approved by the Ethics Committee of the Children's Hospital of Soochow University, and all research were performed in accordance with relevant guidelines and regulations.

Author Contributions:

XLZ participated in study design and protocol development. LD carried out the data analysis and interpretation of data. XQC participated in clinical data collection. JW participated in the design of the study and coordination. XPZ made study design, participated in data analysis, interpretation of data and writing of the manuscript. All authors read and approved the final Manuscript.

Data availability statement:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Comparisons of demographic, nutrition-related characteristics and complications between the groups.

Variable	EUGR group (n = 92)	non-EUGR group (n = 45)	P value
Baseline			
Male	42 (45.7)	20 (44.4)	0.894
Birth weight (g)	1206.90 ± 182.30	1294.78 ± 170.15	0.008
Gestational age (w)	29.67 ± 1.44	30.50 ± 1.41	0.002
Age at admission (h)	2.00 (1.50, 3.75)	3.00 (2.00, 6.00)	0.128
SGA	25 (27.5)	5 (11.1)	0.030
NRDS	42 (45.7)	16 (35.6)	0.261
Neonatal pneumonia	77 (83.7)	8 (84.4)	0.911
Neonatal asphyxia	29 (31.5)	12 (6.7)	0.560
Nutrition-related characteristics			
Hospital stay (d)	59.5 ± 20.13	48.91 ± 15.21	0.003
Feeding intolerance	41 (44.6)	8 (17.8)	0.002
Time of minimum weight (d)	5.00 (3.00, 7.00)	5.00 (4.00, 7.00)	0.295
Weight loss rate (%)	6.49 ± 4.78	5.53 (2.60, 8.02)	0.186
Weight gain rate (g/kg/d)	15.01 ± 3.91	16.47 ± 4.55	0.550
Time of return to birth weight (d)	10.07 ± 4.65	10.55 ± 4.25	0.566
Initiation time of amino acid application (d)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.905
Initiation time of oral fat emulsion (d)	3.00 (3.00, 4.00)	3.00 (3.00, 3.50)	0.089
Initiation time of lactation (d)	3.00 (2.00, 6.00)	3.00 (2.00, 4.00)	0.017
Time to reach oral calorie intake of 120 kcal/kg/d (d)	36.00 (28.00, 49.75)	35.00 (26.00, 52.00)	0.689
Duration of intravenous nutrition (d)	45.00 (38.00, 59.00)	41.00 (32.00, 51.00)	0.040
Complications			
Hypebilirubinemia	89 (96.7)	41 (91.1)	0.160
Septicemia	11 (12.0)	5 (11.1)	0.885
Anemia	77 (83.7)	34 (75.6)	0.254
Intracranial bleeding	17 (18.5)	12 (26.7)	0.270
PVL	6 (6.6)	5 (11.1)	0.565
HIE	4 (4.3)	1 (2.2)	0.533
Intracranial infection	6 (6.5)	2 (4.4)	0.921
Pulmonary hemorrhage	5 (5.4)	0 (0.0)	0.172*

Neonatal hypoglycemia	20 (21.7)	4 (8.9)	0.063
Liver dysfunction	7 (7.6)	2 (4.4)	0.483
NEC	5 (5.4)	0 (0.0)	0.172*
PDA	15 (16.3)	3 (6.7)	0.117

Data are presented as No. (%), mean ± standard deviation, or median (interquartile range).

*P value was analyzed by Fisher’s exact test.

SGA: small for gestational age, NRDS: neonatal respiratory distress syndrome, PVL: periventricular leukomalacia, HIE: hypoxic ischemic encephalopathy, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 2. Nutritional status during the hospital stay between the groups.

ble	3rd day			7th day		
	EUGR group	non-EUGR group	P value	EUGR group	non-EUGR group	P value
fluid kg/d)	121.77 ± 28.15	122.04 ± 23.32	0.956	155.23 ± 26.21	158.10 ± 17.08	0.505
ies ied by venous ional py /kg/d)	53.83 ± 12.75	54.17 ± 11.75	0.883	73.42 ± 16.24	74.40 ± 16.15	0.741
ies ied by ɔ /kg/d)	8.30 ± 2.28	8.38 ± 2.91	0.861	9.75 ± 3.10	11.23 ± 2.64	0.007
ies ied by sion /kg/d)	7.51 (0.00, 9.58)	8.45 (1.64, 9.85)	0.282	15.83 (4.52, 19.03)	12.00 (10.19, 12.91)	0.995

Data are presented as No. (%), mean ± standard deviation, or median (interquartile range).

Table 3. Comparisons of total calorie intake and body weight changes between the groups.

Variable	EUGR group	non-EUGR group	P value
Total calorie intake (kcal/kg/d)			
3^{rd} day	57.18 ± 13.49	58.04 ± 13.68	0.726
7^{th} day	84.24 ± 19.58	85.34 ± 17.01	0.750
14^{th} day	96.14 ± 26.03	98.53 ± 21.98	0.597
28^{th} day	108.58 ± 26.74	117.94 ± 24.08	0.049
Body weight (g)			
3^{rd} day	1157.07 ± 173.87	1274.00 ± 185.26	0.000
7^{th} day	1184.10 ± 162.10	1275.60 ± 193.63	0.004
14^{th} day	1307.00 ± 183.05	1372.90 ± 218.50	0.066
28^{th} day	1583.26 ± 264.35	1750.44 ± 259.30	0.001
at discharge	2206.41 ± 290.30	2376.22 ± 345.05	0.003

Data are presented as No. (%), mean ± standard deviation, or median (interquartile range).

Table 4. Independent risk factors for EUGR by multivariate logistic regression analysis

Risk factor	Odds ratio	95% CI	P value
Gestational age	0.573	0.414–0.794	0.001
SGA	3.887	1.222–12.368	0.022
Feeding intolerance	4.632	1.758–12.203	0.002
Calories supplied by amino acids at the 7^{th} day	0.786	0.661–0.934	0.006

SGA: small for gestational age.