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Risk Factors Contributing to Extrauterine Growth Restriction in Very Low Birth Weight Infants

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ABSTRACT

Purpose: Despite advances in neonatal care, extrauterine growth restriction (EUGR) remains common in preterm infants. This retrospective single-center study aimed to determine the incidence and risk factors of EUGR in very low birth weight (VLBW) infants.

Methods: Data were collected concerning VLBW infants with gestational age (GA) <32 weeks between 2011 and 2020. EUGR was defined as a decline in weight z-score >1.2 from birth to discharge, using Fenton growth charts.

Results: Among 331 eligible preterm infants, the prevalence of EUGR at discharge was 71.6%. Infants with EUGR had lower GA and birth weight than those without EUGR. They also underwent prolonged durations of parenteral nutrition, invasive ventilation, and hospitalization. Neonatal morbidities, such as bronchopulmonary dysplasia, patent ductus arteriosus, necrotizing enterocolitis, gastrointestinal surgery, sepsis, and parenteral nutrition-associated cholestasis were more prevalent in the EUGR group. Multivariate analysis identified lower GA and longer time to reach full enteral feeding as independent risk factors, whereas maternal use of antenatal steroids and history of gestational diabetes mellitus were independent protective factors for EUGR.

Conclusion: As VLBW infants are at a high risk of EUGR, continuous attention and efforts to achieve early full enteral nutrition are required to decrease the incidence of EUGR.

Key Words: Extrauterine growth restriction; Infant, very low birth weight; Infant, premature

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INTRODUCTION

Extrauterine growth restriction (EUGR) is prevalent in preterm and very low birth weight (VLBW) infants. The incidence of EUGR varies from 21.7% to 77.2% depending on the definitions employed[1-9]. EUGR is generally defined as an anthropometric measure (mainly

weight) below a cut-off value, often the 10th percentile, based on the postmenstrual age (PMA) of the preterm infant.

Despite improvements in neonatal care for preterm infants, EUGR remains common during and after admission to neonatal intensive care units (NICUs)[10]. Impaired fetal and postnatal growth has been associated with subsequent issues, such as neurodevelopmental delay, hypertension, insulin resistance, and metabolic syndrome[11]. As postnatal growth has a significant effect on neurodevelopmental outcomes[12], continuous growth monitoring is very important for NICU clinicians.

Factors known to influence EUGR include gestational age (GA), birth weight, male sex, small for gestational age (SGA), periods of inadequate nutrition, and morbidities associated with preterm birth, such as respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), gastrointestinal (GI) perforation, retinopathy of prematurity (ROP), sepsis, and bronchopulmonary dysplasia (BPD)[1,5,7-10,13]. Although common factors contributing to EUGR have been identified in previous studies, many are inconsistent across studies because of confounding variables unique to individual hospital practices or patients[13].

Assessment of EUGR in preterm infants has varied among studies, and there is a lack of a consistent definition of EUGR. Current EUGR definitions can be classified into two categories: (1) Cross-sectional: weight at a given time below the 10th percentile, regardless of birth weight, or (2) Longitudinal: weight loss between birth and a given time with various standard deviation thresholds[5]. Zozaya et al.[14] reported that a decrease in the weight z-score from birth to 36 weeks is a more rational definition of EUGR and can predict neurodevelopment.

In this study, we defined EUGR as the change in weight z-score between birth and discharge using the Fenton growth chart as a reference[15]. The objectives of this study were to estimate the incidence of longitudinal EUGR among VLBW infants in a single center and to identify neonatal and maternal risk factors for EUGR in our VLBW cohort.

MATERIALS AND METHODS

1. Study population

This was a single-center retrospective study of VLBW infants with a GA of <32 weeks, who were born at Inje University Haeundae Paik Hospital between January 2011 and December 2020. We excluded infants who died before discharge and those who were discharged after 50 weeks of PMA because the Fenton growth charts are only applicable to infants <50 weeks of PMA. This study was approved by Institutional Review Board (Inje University Haeundae Paik Hospital # 2024-03-025).

2. Data collection and analysis

Data were collected regarding baseline characteristics, including GA, anthropometric measures (weight, height, and head circumference) at birth, sex, SGA, symmetric intrauterine growth restriction, mode of delivery, multiple births, and *in vitro* fertilization. Data were also collected regarding nutrition, including the percentage of maximum weight loss, time to start feeding, time to reach half enteral feeding (60 mL/kg/day), time to reach full enteral feeding (120 mL/kg/day), and duration of parenteral nutrition.

Duration of invasive ventilation and hospitalization, PMA at discharge and postnatal morbidities, including RDS, moderate-to-severe BPD, surgically treated PDA, NEC, GI surgery, sepsis, and parenteral nutrition-associated cholestasis (PNAC), were collected. BPD was defined as a need for oxygen at 36 weeks of PMA. NEC was defined as Bell's criteria stage two or greater. PNAC was defined as those with a direct bilirubin concentration >2.0 mg/dL without other identifiable causes of cholestasis except for parenteral nutrition.

Maternal history including age, weight, body mass index (BMI), antenatal steroid use, gestational diabetes mellitus (GDM), pregnancy-induced hypertension, preterm premature rupture of membranes, fetal distress, and histological chorioamnionitis, were collected.

Weight at discharge was also recorded. To control for variations in gestational and postnatal age, weight at birth and at discharge were converted into z-scores using the Fenton growth chart[15]. To quantify postnatal growth, the difference in z-scores between birth and discharge was calculated. EUGR was defined as a decline in the weight-for-age z-score >1.2 from birth to discharge, using the Fenton growth chart[16,17]. The enrolled infants were categorized into an EUGR group or a non-EUGR group.

3. Nutritional protocol

Though it was varied according to change in guidelines at our unit and the tolerance of individual patients, common nutritional supplementation principles were as follows.

Enteral feeding was initiated on day 1 after birth for hemody-

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namically stable infants, but was postponed for various causes, such as respiratory distress or hemodynamic instability. The starting enteral feeding volume was 10 to 20 mL/kg/day and increased by 10 to 20 mL/kg/day according to the baby's tolerance until full enteral feeding (120 mL/kg/day) was achieved. We fed the VLBW infants either human milk or premature infant formula. After the enteral feeding volume reached 100 mL/kg/day, breastmilk was fortified with a human milk fortifier.

In all VLBW infants, total parenteral nutrition was started within the first few hours after birth. Amino acids were commenced at 0.5 to 1.5 g/kg/day and increased gradually to 3 to 4.5 g/kg/day over a few days. Carbohydrates were started at 7 to 8 g/kg/day and increased to a maximum dose of 15 to 18 g/kg/day according to the baby's tolerance. Lipid solutions were initiated at 0.5 to 1 g/kg/day and increased to a maximum dose of 3.5 g/kg/day.

Parenteral nutrition was discontinued when full enteral feeding was achieved and weight gain was appropriate. When weight gain was poor, parenteral nutrition was maintained until enteral nutrition reached 130 to 160 mL/kg/day.

4. Statistical analysis

Data were analyzed using R Statistical Software v.4.3.3 (R Foundation for Statistical Computing). Qualitative variables were compared using the Chi-squared test or Fisher's exact test for small numbers. Quantitative variables were compared using Student's t-test for normally distributed variables or the Mann-Whitney *U*-test for non-normally distributed variables. For each quantitative variable, normality was tested using the Shapiro-Wilk test. Univariate and multivariate logistic regression analyses were performed to identify risk factors for EUGR. *P*-values <0.05 were considered to be statistically significant.

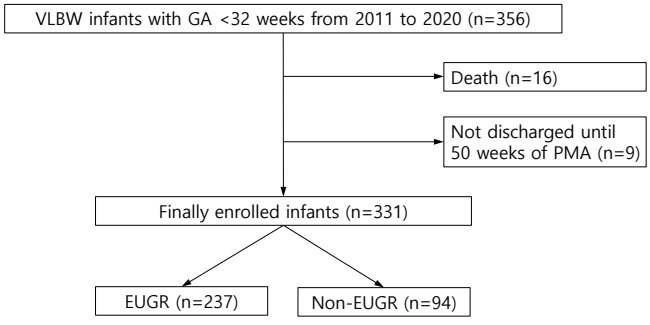

Figure 1. Flow chart of study population. Abbreviations: GA, gestational age; PMA, postmenstrual age; EUGR, extrauterine growth restriction.

RESULTS

During the study period, 356 VLBW infants with GA of <32 weeks were admitted to the NICU (Figure 1). Among them, 16 infants who died and nine infants who were not discharged until 50 weeks PMA were excluded. A total of 331 preterm infants were included in the study. The prevalence of EUGR at discharge was 71.6% (237/331).

Infants in the EUGR group had lower GA (28.0 weeks vs. 29.6 weeks), lower birth weight (1,010 g vs. 1,255 g), and higher birth weight z-score (0.15 vs. –0.18) than infants in the non-EUGR group (Table 1). Height and head circumference at birth were also lower in the EUGR group.

The time to start feeding (4 days vs. 2 days), reach half enteral feeding (18 days vs. 10 days), reach full enteral feeding (31 days vs. 17 days), and duration of parenteral nutrition (37 days vs. 20 days) were longer in the EUGR group than in the non-EUGR group. The durations of invasive ventilation (13 days vs. 4 days) and hospitalization (81 days vs. 61 days) were longer in the EUGR group. PMA at discharge was higher in the EUGR group (39.4 weeks vs. 38.4 weeks). Among postnatal morbidities, the incidence of moderate-to-severe BPD, surgically treated PDA, stage II or higher NEC, GI surgery, sepsis, and PNAC were higher in the EUGR group.

There were no significant differences in maternal age, weight, or BMI between the groups. Among perinatal factors, the use of antenatal steroids (79.3% vs. 90.4%, *P*=0.016) and a history of GDM (7.2% vs. 19.1%, *P*=0.003) were more prevalent in the non-EUGR group than in the EUGR group.

Univariate logistic regression analysis revealed that GA, birth weight, time to start feeding and reach full enteral feeding, BPD, PDA, NEC, GI surgery, sepsis, PNAC, antenatal steroid use, and GDM were significantly associated with EUGR at discharge (Table 2).

Multivariate analysis for EUGR at discharge was adjusted for factors with *P*<0.05 in univariate analyses. In multivariate analysis, lower GA (adjusted odds ratio [adjOR], 0.74; 95% confidence interval [CI], 0.60 to 0.90) and longer time to reach full enteral feeding (adjOR, 1.05; 95% CI, 1.02 to 1.09) were retained as significant independent risk factors for EUGR at discharge. In contrast, maternal use of antenatal steroids (adjOR, 0.31; 95% CI, 0.12 to 0.79) and maternal history of GDM (adjOR, 0.20; 95% CI, 0.08 to 0.52) were significant independent protective factors for EUGR at discharge.

DISCUSSION

This study explored the incidence and risk factors for EUGR in VLBW infants at a single center. The incidence of EUGR varies from 21.7% to 77.2% depending on the definitions employed[1-9]. According to data from the Vermont Oxford Network (2013), 50.3% of VLBW infants are discharged with a body weight below the 10th percentile[2]. In Korea, Lee et al.[8] reported that the inci-

Table 1. Clinical Characteristics and Maternal Factors of 331 Infants according to EUGR at Discharge

Characteristic	EUGR (n=237)	Non-EUGR (n=94)	*P*-value
Baseline characteristics			
Gestational age (wk)	28.0 (26.4 to 29.0)	29.6 (28.1 to 30.5)	0.000
Birth weight (g)	1010 (820 to 1210)	1255 (990 to 1360)	0.000
Birth height (cm)	36.0 (33.5 to 38.0)	38.0 (35.0 to 39.9)	0.000
Birth head circumference (cm)	25.8 (24.0 to 27.0)	27.0 (25.5 to 28.0)	0.000
Weight z-score	0.15 (–0.35 to 0.49)	–0.18 (–0.6 to 0.3)	0.001
Male sex	108 (45.6)	50 (53.2)	0.259
SGA	14 (5.9)	9 (9.6)	0.239
Mode of delivery (vaginal delivery)	41 (17.3)	13 (13.8)	0.545
Multiple birth	106 (44.7)	47 (50)	0.456
IVF	56 (23.6)	26 (27.7)	0.532
Nutrition			
Maximum weight loss (%)	10.8 (7.4 to 14.0)	10.7 (7.9 to 13.2)	0.658
Time to start feeding (d)	4 (2 to 5)	2 (2 to 3)	0.000
Time to reach half enteral feeding (d)	18 (12 to 26)	10 (7 to 16)	0.000
Time to reach full enteral feeding (d)	31 (22 to 45)	17 (12 to 24)	0.000
Duration of parenteral nutrition (d)	37 (28 to 52)	20 (15 to 30)	0.000
Morbidities			
Duration of invasive ventilation (d)	13 (5 to 32)	4 (2 to 13)	0.000
Duration of hospitalization (d)	81 (65 to 106)	61 (54 to 78)	0.000
PMA at discharge (wk)	39.4 (38.0 to 41.6)	38.4 (37.5 to 39.8)	0.000
RDS	235 (99.2)	90 (95.7)	0.057
BPD (moderate-to-severe)	83 (35.0)	14 (14.9)	0.000
PDA (surgically treated)	44 (18.6)	6 (6.4)	0.006
NEC (stage II or higher)	54 (22.8)	10 (10.6)	0.018
GI surgery	40 (16.9)	4 (4.3)	0.002
Sepsis	92 (38.8)	16 (17.0)	0.000
PNAC	59 (24.9)	6 (6.4)	0.000
Maternal factors			
Maternal age	34 (31 to 36)	34 (32 to 37)	0.113
Weight difference between pregnancy (kg)	8 (6 to 11)	8 (6 to 11)	0.555
BMI difference between pregnancy (kg/m^2)	3.0 (2.1 to 4.3)	3.2 (2.4 to 4.1)	0.485
Antenatal steroid	188 (79.3)	85 (90.4)	0.016
GDM	17 (7.2)	18 (19.1)	0.003
Pregnancy-induced hypertension	42 (17.7)	19 (20.2)	0.711
Preterm premature rupture of membranes	143 (60.3)	59 (62.8)	0.777
Fetal distress	72 (30.4)	30 (31.9)	0.888
Histologic chorioamnionitis	121 (51.1)	49 (52.1)	0.957

Values are expressed as number (%) or median (interquartile range).
Abbreviations: EUGR, extrauterine growth restriction; SGA, small for gestational age; IVF, *in vitro* fertilization; PMA, postmenstrual age; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; GI, gastrointestinal; PNAC, parenteral nutrition-associated cholestasis; BMI, body mass index; GDM, gestational diabetes mellitus.

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Table 2. Factors Associated with EUGR at Discharge

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	adjOR*	95% CI	*P*-value
Gestational age	0.63	0.54–0.73	0.000	0.74	0.60–0.90	0.003
Time to start feeding	1.23	1.09–1.39	0.001	1.06	0.93–1.19	0.387
Time to reach full feeding	1.08	1.05–1.11	0.000	1.05	1.02–1.09	0.004
BPD	3.08	1.64–5.77	0.000	1.05	0.49–2.25	0.904
PDA	3.34	1.37–8.14	0.008	1.37	0.45–4.16	0.574
NEC	2.48	1.20–5.11	0.014	0.44	0.16–1.25	0.124
GI surgery	4.57	1.59–13.15	0.005	1.23	0.31–4.87	0.773
Sepsis	3.09	1.70–5.62	0.000	1.86	0.92–3.79	0.086
PNAC	4.86	2.02–11.69	0.000	1.01	0.32–3.20	0.990
Antenatal steroid	0.41	0.19–0.86	0.020	0.31	0.12–0.79	0.014
GDM	0.33	0.16–0.67	0.002	0.20	0.08–0.52	0.001

*Adjusted for gestational age, time to start feeding, time to reach full enteral feeding, BPD, PDA, NEC, GI surgery, sepsis, PNAC, antenatal steroid, and GDM.
Abbreviations: EUGR, extrauterine growth restriction; OR, odds ratio; CI, 95% confidence interval; adjOR, adjusted odds ratio; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; GI, gastrointestinal; PNAC, parenteral nutrition-associated cholestasis; GDM, gestational diabetes mellitus.

dence of EUGR among 2,799 surviving VLBW infants was 45.9%, with the definition of EUGR as a change in z-score from birth to discharge >1.28 using the Fenton chart. In another study in Korea, Kim et al.[9] reported that among 1,356 extremely preterm infants, the incidence of EUGR was 73.8%, with the definition of EUGR as a decreased z-score >1 using the Fenton growth chart. In this study, the incidence of EUGR was 71.6% (237/331) based on the definition of EUGR as a decline in weight z-score >1.2 from birth to discharge, using the Fenton growth chart[16,17]. The incidence of EUGR was higher than previous studies involving VLBW infants[2,8], and similar to a study involving extremely preterm infants[9]. Since nutritional parameters such as calorie intake by enteral and parenteral nutrition were not investigated in this or previous studies, there are limitations to comparisons. This study included a number of patients from an older cohort over the past 10 years, indicating a lack of concern regarding nutrition in the past, which is speculated to be attributed to delayed nutritional advancements. Recently, nutritional strategies have been changed in terms of early aggressive feeding advancement and providing higher protein content depending on the patients' conditions.

Factors known to influence EUGR are GA, birth weight, male sex, SGA, periods of inadequate nutrition, and morbidities associated with preterm birth such as RDS, PDA, NEC, GI perforation, ROP, sepsis, and BPD[1,5,7-10,13]. Although common factors contributing to EUGR have been identified in previous studies, many factors are inconsistent across studies because of confounding variables unique to individual hospital practices or patients[13]. In our study, EUGR was associated with lower GA, lower birth weight, longer time to start feeding, and longer time to reach full enteral feeding (120 mL/kg/day). The EUGR group developed BPD, PDA, NEC, GI surgery, sepsis, and PNAC more frequently. The EUGR group also had longer durations of parenteral nutrition, invasive ventilation, and hospitalization. These findings are consistent with those of the aforementioned studies. More immature and sicker infants may have difficulty advancing feeding and have increased metabolic demands, resulting in malnutrition and poor postnatal growth. Lee et al.[8] reported that SGA was more frequent in a postnatal growth failure (PGF) group than a non-PGF cohort (44.5% vs. 17.1%) which included 2,799 VLBW infants of any GA. In contrast, SGA was similar in both groups in this study (5.9% vs. 6.9%) which included 331 VLBW infants with GA <32 weeks. A considerable number of SGA infants were excluded from this study, resulting in the different results.

After adjusting for potential confounding variables, lower GA (adjOR, 0.74) and longer time to reach full enteral feeding (adjOR, 1.05) were associated with an increased risk of EUGR in this study. Longer time to reach full enteral feeding has also been reported as a risk factor for EUGR in several studies[5,7-9]. This finding also supports the findings in previous studies that emphasized aggressive nutritional support to improve postnatal growth[18,19]. Attention to achieving early full enteral nutrition is necessary to prevent EUGR.

In contrast, antenatal steroid use (adjOR, 0.31) and GDM

(adjOR, 0.20) were associated with a reduced risk of EUGR. Clark et al.[1] reported that antenatal steroids appear to have a small but significant protective effect (adjOR, 0.84). The use of antenatal steroids may stimulate pulmonary maturation and facilitate PDA closure, which may reduce the severity of RDS, duration of mechanical ventilation, and prevalence of BPD. Zhang et al.[20] reported that women with GDM during twin pregnancies and receiving insulin therapy may have a higher risk of developing EUGR. However, several studies that investigated risk factors, including perinatal factors, reported no difference in GDM between EUGR and non-EUGR groups[5,8,9].

This study had certain limitations. In this retrospective observational study, the cohort included a wide range of GAs and birth weights, and as a single-center study, the generalizability of the data is limited. Since this study included a population with a wide range of birth dates, there was a difference in incidence of EUGR over time. When comparing a subgroup of 187 infants (from 2011 to 2015) and 144 infants (from 2016 to 2020), the incidence of EUGR was significantly decreased from 86.1% to 52.8% (P=0.000). EUGR was more prevalent in the past probably due to a lack of concern surrounding nutrition, and as nutritional strategies have improved, the incidence of EUGR has decreased. Such changes in strategies of nutritional support may have influenced our results and this represents one limitation of this study in that we did not investigate nutritional practices including calorie intake via enteral and parenteral nutrition. Additional research regarding postnatal growth according to changes in nutritional support is in progress. However, this study remains meaningful because there has been very limited research concerning EUGR in large numbers of VLBW infants.

In summary, we investigated the incidence and risk factors for EUGR in >300 VLBW infants at a single center over 10 years. We also identified GA and number of days to achieve enteral feeding of 120 mL/kg as independent risk factors for EUGR, whereas maternal use of antenatal steroids and history of GDM were independent protective factors for EUGR in VLBW infants. As VLBW infants are at an elevated risk of EUGR, continuous attention and efforts to achieve early full enteral nutrition are required to further decrease the incidence of EUGR.

ARTICLE INFORMATION

Ethical statement

This study was approved by the respective Institutional Review Board (Inje University Haeundae Paik Hospital #2024-03-025). Written informed consent by the patients was waived due to a retrospective nature of our study.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conception or design: M.L.C.

Acquisition, analysis, or interpretation of data: H.S.H.

Drafting the work or revising: H.S.H.

Final approval of the manuscript: All authors read and approved the final manuscript.

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