ORIGINAL ARTICLE

Risk Factors of Extrauterine Growth Restriction in Very Preterm or Very Low Birth Weight Infants

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Background: Extrauterine growth restriction (EUGR) is one of the complications that can arise in preterm neonates, impacting future neurodevelopment and growth.

Objective: To identify the risk factors of EUGR in very preterm (VPT) or very low birth weight (VLBW) infants.

Materials and Methods: A case-control study was conducted at the neonatal intensive care unit (NICU) of Bhumibol Adulyadej Hospital (BAH), Thailand, by reviewing the medical records of VPT or VLBW infants treated at BAH between November 2016 and August 2023. The subjects were divided into EUGR and non-EUGR groups. The primary outcome was the risk factors of EUGR, while the secondary outcome was the characteristics of nutrition support.

Results: Data from 78 infants in the present study group and 156 infants in the control group were analyzed. The risk factors for EUGR were bronchopulmonary dysplasia (BPD) (aOR 2.44, 95% CI 1.08 to 5.50, p=0.03) and the time to regain birth weight of more than seven days (aOR 4.83, 95% CI 2.24 to 10.41, p<0.01). The duration of parenteral nutrient support was significantly longer in the study group at 13.5 days for the study group versus 9.0 days for the control group (p<0.01). The time to reach target enteral feeding of 120 mL/kg/day or more was also slower compared to the control group at 15 days for the study group versus 10 days for the control group (p<0.01).

Conclusion: BPD and delayed weight regain significantly increase the risk of EUGR. Affected infants require prolonged parenteral nutrition and take longer to reach full oral feeding. To reduce this risk, optimizing nutrition, ensuring adequate protein and energy intake, and improving BPD monitoring with evidence-based respiratory and fluid management are essential for better growth outcomes.

Keywords: Extrauterine; Growth restriction; Very preterm; Very low birth weight

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The preterm birth and survival rate have increased in the past decades[1]. Premature neonates are more prone to postnatal growth failure or extrauterine growth restriction (EUGR) than term neonates. A combination of low nutrient storage and preterm complications can cause malnutrition and consequently EUGR, which adversely affects neurodevelopmental outcomes.

EUGR is mostly defined as weight less than tenth percentile at hospital discharge or 36 weeks postmenstrual age (PMA)[2]. The incidence of EUGR varies among different institutes, ranging from 24% to 60% in Europe[3]. The authors' center had an incidence of EUGR at 59.5%.

Currently, the definition of EUGR as a decline in weight-for-age z scores (WAZ) is gaining popularity, considering the divergent antenatal status and medical conditions among individuals. Studies found no association of poor neurodevelopment outcome using weight of less than the tenth percentile as compared to a decreased in WAZ[4]. A decline in WAZ can further be classified as mild for 0.8 to 1.2 SD, moderate for greater than 1.2 to 2.0 SD, and severe for greater than 2.0 SD[5].

EUGR has significant impacts on future health. EUGR infants with persisting growth failure at five years of age have a 90% risk of short stature in adulthood[6]. Additionally, EUGR may affect neurodevelopmental outcomes later in life, such as hyperactivity and limited academic skills[7]. Therefore, the present study aimed to evaluate the risk factors of EUGR in very preterm (VPT) and very low birth weight (VLBW) infants.

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Materials and Methods

Study design, participant, and setting

The present study was a case-control study conducted at the neonatal intensive care unit (NICU) of Bhumibol Adulyadej Hospital (BAH) in Bangkok, Thailand. The data were collected from November 2016 to August 2023. The present study was approved by the hospital's Ethic Committee (IRB No.69/66).

VPT, as gestational age of less than 32 weeks, and/or VLBW as birth weight of less than 1,500g, infants were included into the study. Infants with WAZ that declined by more than 1.2 were classified into EUGR group, while those with WAZ that declined less than 1.2 were placed into the control group[4].

Infants with congenital anomalies such as cleft palate, abdominal wall defect, and esophageal atresia were excluded. Those transferred to BAH later than 36 weeks PMA were also excluded.

Data collection

The data were collected through a review of electronic medical records. Demographic data included maternal information such as age, serology such as syphilis, HIV, and hepatitis B infection, parity, and pregnancy complications such as gestational hypertension and diabetes. Infant details, such as gender, gestational age, body weight, length, and head circumference at birth were also recorded. Additionally, records of morbidities such as bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), sepsis, necrotizing enterocolitis (NEC), and others were collected. Nutritional support, including both parenteral and enteral nutrition was recorded.

Definitions, anthropometric measurements, and diagnostic criteria

EUGR in the present study is defined as a decline in WAZ of more than 1.2 from birth to 36 weeks' post-conceptual age (PCA) or discharge, whichever comes earlier. Age-and gender-specific birth weight, length, and head circumference were converted to percentiles and z-scores using the Fenton 2013 Preterm Growth Chart[8]. Maximum weight loss was calculated as a percentage using the following equation:

Maximum weight loss =
[(birth weight – lowest weight) / birth weight] × 100

Average protein, fat, and glucose intake via the parenteral route were calculated using formulas, for example:

Average protein =
sum of parenteral protein intakes / number of days

Late onset sepsis (LOS) was defined as either a positive blood culture or cerebrospinal fluid culture with clinical signs appearing later than 72 hours of age. Severe RDS was defined as clinical signs necessitating invasive mechanical ventilator support. BPD diagnosis and severity grading were determined according to Jensen criteria 2019[9]. Hemodynamic significant patent ductus arteriosus (hsPDA) was defined as a PDA seen in echocardiography accompanied by clinical signs of hemodynamic instability. Established NEC was defined as modified Bell's staging grade IIa or above[10].

Statistical analysis and sample size estimation

The sample size was calculated based on Starc's study[11]. A statistical power of 85% and type one error of 0.05 were used. The calculated sample size with a 2 to 1 ratio was 78 subjects in the study group and 156 subjects in the control group. Random sampling was used.

The data were analyzed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean ± standard deviation, while non-normally distributed data were expressed as median (P25, P75). The two independent sample t-test and Mann-Whitney U test were used for continuous variables. Chi-square and Fisher's exact test were used for categorical variables. Logistic regression analysis was used to evaluate the risk factors. Significant indices identified by univariable analysis were further analyzed using multivariable analysis. All the p-values were two-sided, and the p-value of less than 0.05 was considered statistically significant.

Results

The data from 273 VPT or VLBW infants were collected from BAH neonate records. Nine subjects were excluded. For the analysis, simple random sampling was applied to select subjects for the control and study groups. A computer-generated randomization tool was used to randomly select from 234 subjects, with 156 subjects in the control group and 78 subjects in the study group (Figure 1).

Maternal data revealed a higher rate of vaginal delivery in the study group compared to the control group at 53.8% versus 39.1%. In the EUGR group, infants had a lower gestational age and longer length of stay. The authors found no statistically significant

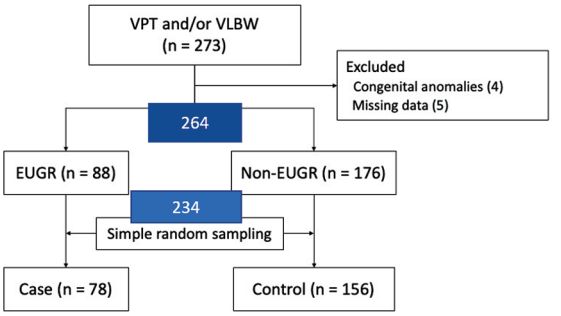

Figure 1. Study flow.

VPT=very preterm; VLBW=very low birth weight; EUGR=extrauterine growth restriction

difference in utero growth status (Table 1).

All recorded preterm complications were distinctly found in the EUGR group with a higher rate of LOS, severe RDS, BPD, hsPDA, and NEC in the study group compared to the control group, which were deemed statistically significant (Table 2).

The present study showed better anthropometric z score and percentile at birth in the study group compared to the control group (Table 3). However, those with EUGR experienced more weight loss ($p<0.01$), with 85.9% taking longer time than seven days to regain birth weight ($p<0.01$). In addition, the study group required a longer duration of parenteral nutrition and a longer time to reach target enteral feeding compared to the control group.

In the multivariable analysis (Table 4), EUGR was found to be independently associated with BPD (adjusted OR 2.44, $p=0.03$) and the time to regain birth weight exceeding seven days (adjusted OR 4.83, $p<0.01$).

Discussion

In the present study, all complications of prematurity were found more in the study group compared to the control group. This may suggest that the severity of illness in infants may correlate with the likelihood of EUGR. The authors found a two-fold increased risk of EUGR with BPD (95% CI 1.08 to 5.50, $p=0.03$). Similarly, Wang et al. reported moderate to severe BPD as a risk factor of EUGR (OR 3.11, 95% CI 1.52 to 6.37)[12]. Lyu et al. also found an increased risk of EUGR in BPD patients (adjusted OR 1.55, 95% CI 1.26 to 1.89)[13]. BPD is a chronic respiratory illness that requires higher energy expenditure, so inadequate nutrient intake can lead to undernutrition and growth failure.

In the control group, the weight, length, and head circumference z scores at birth appeared to be lower than those in the study group, but this trend reversed at PCA 36 weeks. A previous study by Lyu et al. showed a greater decrease in WAZ in neonates classified as large-for-gestation compared to those classified as appropriate-for-gestation at 41.9% versus 18.1%[13]. The reversal of growth trajectories underscores the dynamic nature of postnatal

Table 1. Demographics and clinical data between EUGR and non-EUGR groups

	EUGR (n=78)	Non-EUGR (n=156)	p-value
Maternal			
Age (year); mean±SD	28.8±6.8	28.69±7.1	0.93
Nulliparity; n (%)	33 (42.3)	60 (38.5)	0.57
Twin; n (%)	6 (7.7)	23 (14.7)	0.12
No antenatal care; n (%)	12 (15.4)	25 (16.0)	0.90
Abnormal serology; n (%)	3 (3.8)	8 (5.1)	0.66
Vaginal delivery; n (%)	42 (53.8)	61 (39.1)	0.03
Hypertension; n (%)	13 (16.7)	41 (26.3)	0.10
Diabetes mellitus; n (%)	15 (19.2)	29 (18.6)	0.91
Antenatal medications; n (%)			
• Corticosteroids	53 (67.9)	121 (77.6)	0.11
• Magnesium	21 (26.9)	52 (33.3)	0.32
• Antibiotics	29 (37.2)	69 (44.2)	0.30
Infants			
GA (week); median [IQR]	29 [27, 31]	30 [29, 31]	<0.01
Male; n (%)	43 (55.1)	81 (51.9)	0.64
IUGR; n (%)	10 (12.8)	37 (23.7)	0.05
Measurement at birth			
• Weight (g); mean±SD	1,202±391	1,288±293	0.06
• Length (cm); mean±SD	38±5	39±4	0.13
• HC (cm); median [IQR]	26 [24, 28]	27 [26, 28]	0.08
Length of stay (day); median [IQR]	63 [43, 93]	44 [33, 65]	<0.01

EUGR=extrauterine growth restriction; GA=gestational age; IUGR=intrauterine growth restriction; HC=head circumference; SD=standard deviation; IQR=interquartile range

Table 2. Preterm complications between EUGR and non-EUGR groups

	EUGR (n=78) n (%)	Non-EUGR (n=156) n (%)	OR (95% CI)	p-value
Late onset sepsis	16 (20.5)	14 (9.0)	2.62 (1.20 to 5.69)	0.01
RDS	60 (76.9)	111 (71.2)	1.35 (0.72 to 2.54)	0.35
Severe RDS	31 (39.7)	35 (22.4)	2.28 (1.27 to 4.11)	0.01
BPD	23 (29.5)	18 (11.5)	3.21 (1.61 to 6.40)	<0.01
hsPDA	43 (55.1)	52 (33.3)	2.46 (1.41 to 4.29)	<0.01
NEC	7 (9.0)	4 (2.6)	3.75 (1.06 to 13.21)	0.03
IVH	31 (39.7)	47 (30.1)	1.53 (0.87 to 2.70)	0.14

EUGR=extrauterine growth restriction; OR=odds ratio; CI=confidence interval; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; hsPDA=hemodynamic significant patent ductus arteriosus; NEC=necrotizing enterocolitis; IVH=intraventricular hemorrhage

Table 3. Growth and nutrition status between groups

	EUGR (n=78)	Non-EUGR (n=156)	p-value
Growth			
At birth z scores; mean±SD			
• Weight-for-age	−0.24±0.94	−0.69±0.97	<0.01
• Length-for-age	0.22±1.36	−0.32±1.39	0.01
• HC-for-age	−0.25±1.32	−0.80±1.33	<0.01
At birth percentile; median [IQR]			
• Weight	42.8 [17.7, 58.8]	30.0 [10.3, 52.5]	<0.01
• Length	60.2 [28.4, 88.3]	37.4 [12.3, 69.5]	0.01
• HC	45.1 [18.6, 72.7]	25.5 [6.9, 51.4]	<0.01
At PCA 36 weeks or discharge z scores; mean±SD			
• Weight-for-age	−1.97±0.98	−1.34±1.04	<0.01
• Length-for-age	−0.84±1.40	−0.57±1.41	0.19
• HC-for-age	−1.52±1.23	−0.98±1.06	<0.01
At PCA 36 weeks or discharge percentile; median [IQR]			
• Weight	2.1 [0.5, 7.6]	12.7 [2.0, 29.2]	<0.01
• Length	17.9 [4.1, 54.4]	34.3 [6.2, 66.7]	0.13
• HC	8.9 [2.1, 23.6]	13.6 [4.1, 42.0]	<0.01
Maximum weight loss; mean±SD	10.1±4.1	7.3±3.7	<0.01
Time to gain birth weight >7 days; n (%)	67 (85.9)	91 (58.3)	<0.01
Nutrition			
Parenteral (PN)			
• Duration (day); median [IQR]	13.5 [7.8, 22.0]	9.0 [5.0, 13.0]	<0.01
• Average protein in 1st week (g/kg/day); median [IQR]	2.68 [2.0, 3.17]	2.59 [1.73, 3.07]	0.35
• Average fat in 1st week (g/kg/day); mean±SD	1.75±0.84	1.80±0.98	0.71
• Average glucose in 1st week (g/kg/day); median [IQR]	6.92 [5.77, 8.83]	6.92 [5.89, 8.83]	0.85
Enteral (EN)			
• Initiate EN after 1st DOL; n (%)	12 (15.4)	13 (8.3)	0.10
• Time to EN ≥120 mL/kg/day (day); median [IQR]	15 [10, 24]	10 [7, 15]	<0.01

EUGR=extrauterine growth restriction; HC=head circumference; PCA=postconceptual age; DOL=day of life; SD=standard deviation; IQR=interquartile range

Table 4. Multivariable analysis of selected risk factors for EUGR

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Time to gain weight >7 days	4.35 (2.13 to 8.87)	<0.01	4.83 (2.24 to 10.41)	<0.01
Late onset sepsis	2.62 (1.20 to 5.69)	0.01	1.83 (0.78 to 4.31)	0.17
Severe RDS	2.28 (1.27 to 4.11)	0.01	1.53 (0.76 to 3.08)	0.24
BPD	3.21 (1.61 to 6.40)	<0.01	2.44 (1.08 to 5.50)	0.03
hsPDA	2.46 (1.41 to 4.29)	<0.01	1.69 (0.89 to 3.24)	0.11
Necrotizing enterocolitis	3.75 (1.06 to 13.21)	0.03	3.18 (0.81 to 12.51)	0.10

RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; hsPDA=hemodynamic significant patent ductus arteriosus; OR=odds ratio; CI=confidence interval

growth and its dependency on effective nutritional interventions. Neonates with poorer prenatal growth warrant increased monitoring to mitigate EUGR risk.

Normally, most newborn will have acceptable postnatal weight loss of about 7% to 10% during the first two weeks of life[14]. The present study revealed that EUGR infants lost more weight than non-EUGR infants at 10.1±4.1 versus 7.3±3.7 (p<0.01). In contrast, Wang et al. conducted a study on EUGR in BPD infants and reported no different in maximum weight loss between groups at 7% in EUGR versus 6.3% in control (p=0.16)[15]. However, they found a longer time to regain birth weight in

the EUGR group compared to the control group at 10 days versus 9 days (p=0.03)[15]. Wang et al. also reported an increased risk of EUGR with longer days to regain birthweight (OR 1.19, 95% CI 1.12 to 1.27, p<0.01)[12]. The authors' study found that infants who took more than seven days to regain birth weight were almost five times more likely to be at risk of EUGR (p<0.01). This highlights the importance of emphasizing postnatal nutrition support.

In the authors' center, strategies were implemented to improve growth outcomes including the establishment of an in-house nutritional protocol. More than two-thirds of infants in the present study received enteral feeding within the first day of life.

In the authors' center, strategies like an in-house nutritional protocol were implemented to improve growth outcomes, and more than two-thirds of infants received enteral feeding within the first day of life. There was no statistically significant difference in the initiation of enteral feeding. However, EUGR infants appeared to require a longer time to reach target enteral feeding (p<0.01). Correspondingly, a previous study conducted by Shen et al. found a slower time to reach full enteral feeding in the EUGR group compared to the non-EUGR group at 30 days versus 21 days (p<0.01)[16]. The study by Wang et al. reported an association between EUGR and the number of days to achieve target oral caloric intake (OR 1.03, 95% CI 1.01 to 1.04, p<0.01)[15]. Policymakers should prioritize early nutritional support and establish standardized enteral feeding protocols for high-risk populations, particularly those with EUGR, supported by a multidisciplinary approach and enhanced healthcare provider training.

The strength of the present study lies in its well-defined population and the application of multivariable analysis to identify independent risk factors for EUGR. This approach not only enhances the reliability of the findings by controlling for confounding variables but also provides a robust framework for understanding the key determinants of EUGR, ensuring clinical relevance and precision. However, the present study had limitations that it was a single-center study. The authors collected data on parenteral nutrition during the first week of life. Therefore, a direct relationship between the components of parenteral nutrition support and EUGR cannot be established clearly. Moreover, the study assesses outcomes primarily at 36 weeks PCA or discharge, which may not capture long-term growth and developmental issues associated with EUGR. Since EUGR is a chronic process, further studies with longer data collection periods may be beneficial.

Conclusion

BPD and a longer time to regain birth weight contributed to the occurrence of EUGR. In addition, extrauterine growth failure can affect all infants regardless of their intrauterine growth status. Infants needing longer parenteral nutritional support and experiencing delays in achieving target enteral feeding were also associated with EUGR. Therefore, customized nutritional support should be considered based on the medical condition of each infant.

What is already known about this topic?

Imbalance between nutritional support and energy expenditure can result in EUGR.

What does this study add?

The authors found that BPD and a longer time to regain birth weight had associated with higher risk of future EUGR, especially longer than seven days. This may be used as a monitoring point for physicians to improve on nutrition plans.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. AlQurashi MA. Survival rate of very low birth weight infants over a quarter century (1994-2019): A single-institution experience. J Neonatal Perinatal Med 2021;14:253-60.
2. Sakurai M, Itabashi K, Sato Y, Hibino S, Mizuno K. Extrauterine growth restriction in preterm infants of gestational age <or=32 weeks. Pediatr Int 2008;50:70-5.
3. El Rafei R, Jarreau PH, Norman M, Maier RF, Barros H, Reempts PV, et al. Variation in very preterm

extrauterine growth in a European multicountry cohort. Arch Dis Child Fetal Neonatal Ed 2021;106:316-23.
4. Fenton TR, Cormack B, Goldberg D, Nasser R, Alshaikh B, Eliasziw M, et al. "Extrauterine growth restriction" and "postnatal growth failure" are misnomers for preterm infants. J Perinatol 2020;40:704-14.
5. Goldberg DL, Becker PJ, Brigham K, Carlson S, Fleck L, Gollins L, et al. Identifying malnutrition in preterm and neonatal populations: Recommended indicators. J Acad Nutr Diet 2018;118:1571-82.
6. Martínez-Jiménez MD, Gómez-García FJ, Gil-Campos M, Pérez-Navero JL. Comorbidities in childhood associated with extrauterine growth restriction in preterm infants: a scoping review. Eur J Pediatr 2020;179:1255-65.
7. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med 1991;325:231-7.
8. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59. doi: 10.1186/1471-2431-13-59.
9. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach. Am J Respir Crit Care Med 2019;200:751-9.
10. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179-201.
11. Starc M, Giangreco M, Centomo G, Travan L, Bua J. Extrauterine growth restriction in very low birth weight infants according to different growth charts: A retrospective 10 years observational study. PLoS One 2023;18:e0283367.
12. Wang YS, Shen W, Wu F, Mao J, Liu L, Chang YM, et al. Factors influencing extrauterine growth retardation in singleton-non-small for gestational age infants in China: A prospective multicenter study. Pediatr Neonatol 2022;63:590-8.
13. Lyu Y, Zhu D, Wang Y, Jiang S, Lee SK, Sun J, et al. Current epidemiology and factors contributing to postnatal growth restriction in very preterm infants in China. Early Hum Dev 2022;173:105663. doi: 10.1016/j.earlhumdev.2022.105663.
14. Jochum F, Moltu SJ, Senterre T, Nomayo A, Goulet O, Iacobelli S. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Fluid and electrolytes. Clin Nutr 2018;37:2344-53.
15. Wang L, Lin XZ, Shen W, Wu F, Mao J, Liu L, et al. Risk factors of extrauterine growth restriction in very preterm infants with bronchopulmonary dysplasia: a multi-center study in China. BMC Pediatr 2022;22:363. doi: 10.1186/s12887-022-03405-z.
16. Shen W, Zheng Z, Lin XZ, Wu F, Tian QX, Cui QL, et al. Incidence of extrauterine growth retardation and its risk factors in very preterm infants during hospitalization: a multicenter prospective study. Zhongguo Dang Dai Er Ke Za Zhi 2022;24:132-40.