

Incidence of and Risk Factors for Extrauterine Growth Restriction in Preterm Infants with Gestational Age Less Than 32 Weeks or Birth Weight Less Than 1,500 Grams

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ABSTRACT

OBJECTIVE To determine the incidence and risk factors for extrauterine growth restriction (EUGR) in preterm infants with gestational age (GA) less than 32 weeks or birth weight (BW) less than 1,500 grams.

METHODS A retrospective cohort study reviewed preterm infants admitted at Chiang Mai University Hospital between January 1, 2017, and December 31, 2020. EUGR was defined as weight below the 10th percentile at 36 weeks postmenstrual age based on the Fenton growth chart. Data were analyzed, with a *p*-value of less than 0.05 considered statistically significant. Multivariate regression analysis was adjusted for confounding variables.

RESULTS Among 310 eligible infants, 201 (64.8%) were diagnosed with EUGR. All of 76 SGA infants (100.0%) were EUGR. Significant risk factors included proven sepsis (OR 3.90, 95%CI 1.13-13.45, *p* = 0.03), diuretic use (OR 3.62, 95%CI 1.47-8.91, *p* = 0.005), definite NEC (OR 3.54, 95%CI 1.60-7.83, *p* = 0.002), maternal gestational hypertension (OR 2.36, 95%CI 1.28-4.35, *p* = 0.006), and multiple births (OR 1.85, 95%CI 1.04-3.28, *p* = 0.04). Nutritional risk factors were delayed full enteral feeding (OR 1.08, 95%CI 1.03-1.12, *p* = 0.001) and higher initial glucose infusion rate (GIR) in TPN (OR 1.28, 95%CI 1.11-1.48, *p* = 0.001). Infants with EUGR had longer hospital stays and higher hospital costs than non-EUGR infants. Multivariate analysis showed significant risks including definite NEC (OR 2.45, 95%CI 1.01-5.96, *p* = 0.049), maternal gestational hypertension (adjusted OR 2.79, 95%CI 1.46-5.33, *p* = 0.002), and multiple births (adjusted OR 2.29, 95%CI 1.24-4.24, *p* = 0.008).

CONCLUSIONS Multiple births, maternal gestational hypertension, SGA status, and NEC were associated with a higher risk of EUGR in preterm infants less than 32 weeks or VLBW. Providing proper antenatal care for mothers with multiple pregnancies or gestational hypertension, along with optimized postnatal care, can help improve growth outcomes and reduce the incidence of EUGR in these infants.

KEYWORDS extrauterine growth restriction, preterm infant, very low birth weight

INTRODUCTION

Over the past few decades, the survival rates of very low birth weight (VLBW) infants, those

with birth weights less than 1,500 grams, have increased. However, these infants still face a risk of growth and neurodevelopmental problems

despite their higher overall survival rates (1). Extrauterine growth restriction (EUGR), particularly in VLBW preterm infants, is a prevalent issue that affects healthcare costs, length of hospital stays, and long-term morbidity, including cognitive dysfunction, behavioral problems, and metabolic diseases (2-4).

The incidence of EUGR among VLBW infants varies by country and is influenced by the quality and the competency of neonatal intensive care units (NICUs). In Asian countries, the incidence ranges from 67-72%, which is comparable to European countries where it ranges from 51-73%, but notably higher than in the U.S., where the incidence is 28% (5-9). This variation is likely due to differences in neonatal care practices, nutrition management strategies, and the availability of advanced medical technologies, all of which influence growth outcomes in preterm infants across regions.

Several biological and epidemiological factors contribute to the slower growth of Asian populations compared to Caucasians. One key factor is genetic predisposition. Studies have shown that differences in body composition, including lower lean body mass and higher fat percentage at birth, are more common in Asian infants, which may result in slower postnatal growth rates (10). Additionally, maternal nutritional status during pregnancy in many Asian countries can be suboptimal due to cultural dietary practices, economic factors, or limited access to healthcare, which can affect fetal growth and lead to smaller birth sizes (11). Furthermore, the prevalence of gestational diabetes and hypertension is higher in Asian populations, conditions known to impact fetal growth (12). Another factor is the higher incidence of preterm births in some Asian countries, which increases the likelihood of EUGR in preterm infants (13).

The Fenton growth curve is widely used to define EUGR in preterm infants, including those in Asian populations. It serves as a standardized tool for monitoring growth based on gestational age and birth weight, comparing postnatal growth to intrauterine growth patterns (14). However, the curve was developed using data predominantly from Western populations, which may not fully represent the growth characteristics of Asian infants who generally have lower birth weights and smaller body sizes at the same gestational ages

compared to their Caucasian counterparts (15, 16). Despite these limitations, the Fenton growth curve remains a valuable tool for growth monitoring and continues to be used in our institution for assessing growth in VLBW infants.

Previous studies have identified several prenatal and postnatal risk factors for EUGR. Prenatal risk factors include advanced maternal age (over 35 years), multiple births, and pregnancy complications such as placental abruption, maternal gestational hypertension, and gestational diabetes (1, 17). Postnatal risk factors include general issues such as nutritional deficiencies and being small for gestational age (SGA), as well as comorbidities such as respiratory distress syndrome, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD) (1, 9, 18).

No study has yet examined the incidence and risk factors of EUGR in Thailand, limiting the development of strategies to prevent or reduce it. Since the incidence and risk factors for EUGR differ between countries due to population differences and healthcare practices and no data is available for Thailand, further research is needed. This study aims to identify the incidence and risk factors of EUGR in VLBW infants in Thailand.

METHOD

This retrospective cohort study utilized data gathered from electronic medical records. Participants included preterm infants with a gestational age (GA) of less than 32 weeks or a birth weight of less than 1,500 grams (very low birth weight; VLBW) who were born in a hospital or admitted within 48 hours after birth at Chiang Mai University Hospital, Thailand, a tertiary care hospital, between January 1, 2017, and December 31, 2020.

Patients with chromosomal abnormalities, major congenital malformations (including critical congenital heart conditions and surgical congenital gastrointestinal conditions), TORCH infections, and those who died before 36 weeks postmenstrual age (PMA) were excluded.

The sample size was calculated using a statistical formula based on a 95% confidence level and a 5% margin of error. This calculation was informed by the study of Peila. (8), which reported an EUGR incidence of 73% in preterm infants with a GA of

less than 30 weeks or a birth weight of less than 1,500 grams. Consequently, the required sample size for our study was determined to be 303 patients.

EUGR was diagnosed when the patient's weight at 36 weeks PMA was less than the 10th percentile according to the Fenton growth chart. Respiratory distress syndrome was diagnosed based on signs of increased work of breathing and a demonstration of fine reticular granularity of lung parenchyma with air bronchograms on chest radiography (19). PDA was diagnosed based on the presence of clinical signs plus abnormal radiographic findings, including increased pulmonary vasculature or cardiomegaly, or on echocardiographic findings of PDA which were treated medically or surgically (20). NEC was diagnosed based on clinical, radiological, and/or histopathological evidence that fulfilled stage II or III of modified Bell's criteria and was treated medically or surgically (21). IVH was detected by a radiologist and graded by Papile's classification as severe as grade III or IV (22). BPD was diagnosed using the definitions from the National Institutes of Health 2018 (23). Resuscitation in the delivery room was defined as one or more of the following procedures: positive pressure ventilation (PPV), chest compression (CPR), intubation, or continuous positive airway pressure. Proven sepsis was defined by the presence of a positive hemoculture and correlated with clinical signs of sepsis. SGA was diagnosed when the patient's birth weight was less than the 10th percentile according to the Fenton growth chart.

According to Chiang Mai University Hospital's feeding guidelines for VLBW infants, these infants are started on a standard intravenous solution containing glucose, amino acid, and calcium gluconate within 24–48 hours after birth, followed by parenteral nutrition the next day with initial fluids of 60–100 mL/kg/day, initial protein of 2–3 g/kg/day, initial glucose of 4–6 mg/kg/min, and initial lipid of 1–2 g/kg/day. Enteral nutrition is initiated within 48 hours after birth or when the infant is clinically stable, with colostrum (0.5–2 mL) used as mouth care every 8 hours, or more frequently if enteral nutrition cannot be started.

Statistical analysis

Data were analyzed using IBM SPSS statistics for Windows, version 26 (SPSS, Armonk, NY, USA). A *p*-value of less than 0.05 was considered statis-

tically significant. Demographic data of infants with and without EUGR were compared using the Student's *t*-test for continuous variables and the Chi-square test for categorical variables, while the Mann-Whitney *U* test or the *t*-test was utilized for continuous variables in univariate analysis.

Multivariate regression analysis was used to adjust for potentially confounding variables based on significant data from the univariate logistic analysis of factors associated with EUGR. Analysis of covariance was used for continuous outcome variables, and logistic regression was used for dichotomous variables. Results are reported for both analyses if the findings were significantly different. Logistic regression analysis results are expressed as odds ratios (OR) with 95% confidence intervals (CI).

Ethical approval

The study was approved by the Research Ethic Committee Faculty of medicine, Chiang Mai University, under protocol code PED-2564-08082.

RESULTS

A total of 403 preterm infants with GA less than 32 weeks or VLBW were admitted to Chiang Mai University Hospital over four years. Ninety-three infants were excluded due to being referred at more than 48 hours of age, dying before 36 weeks PMA or discharge, having significant congenital anomalies or chromosomal abnormalities, or having a TORCH infection. This left 310 infants enrolled in the study. The data was completely reviewed without missing data.

Among the 310 eligible infants, 201 (64.8%) were diagnosed with EUGR. Additionally, all 76 SGA infants were identified with EUGR (100%). The demographic and clinical characteristics of infants with and without EUGR are shown in Table 1. Significant risk factors associated with EUGR included proven sepsis (OR 3.90, 95%CI 1.13–13.45, *p* = 0.030), diuretic use (OR 3.61, 95%CI 1.47–8.90, *p* = 0.005), definite NEC (OR 3.53, 95%CI 1.60–7.82, *p* = 0.002), maternal gestational hypertension (OR 2.35, 95%CI 1.27–4.34, *p* = 0.006), and multiple births (OR 1.84, 95%CI 1.04–3.27, *p* = 0.040). Nutritional risk factors included longer time to full enteral feeding (OR 1.07, 95%CI 1.02–1.12, *p* = 0.001) and higher GIR started in TPN (OR 1.28, 95%CI 1.10–1.48, *p* = 0.001). Infants with EUGR had

Table 1. Demographic and clinical characteristics of infants with and without extrauterine growth restriction (EUGR)

Factors	EUGR (n=201)	Non EUGR (n=109)	p-value
Male gender, n (%)	99 (49)	55 (50)	0.840
Mean gestational age, weeks ($\pm$ SD)	30.5 ($\pm$ 2.9)	30.0 ($\pm$ 2.5)	0.139
Mean birth weight, grams ($\pm$ SD)	1130 ($\pm$ 328)	1441 ($\pm$ 429)	< 0.001*
Antenatal factors			
Elderly gravida, n (%)	58 (29)	37 (34)	0.353
Multiple births, n (%)	59 (29)	20 (18)	0.034*
Any doses antenatal steroid, n (%)	164 (82)	92 (84)	0.533
Placenta abruption, n (%)	8 (4)	9 (8)	0.114
PROM, n (%)	53 (26)	29 (27)	0.964
Gestational diabetes, n (%)	33 (16)	22 (20)	0.407
Maternal gestational hypertension, n (%)	58 (29)	16 (15)	0.005*
Intrauterine growth restriction, n (%)	38 (19)	0 (0)	< 0.001*
Intrapartum factors			
Mean APGAR score at 5 min, score ($\pm$ SD)	7 ($\pm$ 1)	7 ($\pm$ 1)	0.652
Resuscitation, n (%)	173 (86)	98 (90)	0.331
Postnatal factors			
General Postnatal factors			
- Small for gestational age, n (%)	76 (38)	0 (0)	< 0.001*
- Median NPO time, day (Range)	1 (0-106)	1 (0-21)	0.026*
- Median age at first TPN was started, hour (range)	13 (1-30)	12 (1-70)	0.213
- Mean of initial parenteral protein, gram/kg/day ($\pm$ SD)	2.7 ($\pm$ 1.4)	2.2 ($\pm$ 1.0)	0.091
- Mean of initial parenteral fat, gram/kg/day ($\pm$ SD)	1.1 ($\pm$ 0.4)	0.9 ($\pm$ 0.5)	0.093
- Mean of initial parenteral glucose, mg/kg/min ($\pm$ SD)	5.5 ($\pm$ 1.4)	4.8 ($\pm$ 2.1)	0.001*
- Median TPN duration, day (Range)	9 (1-127)	8 (1-44)	< 0.001*
- Median time to full enteral feeding, day (range)	11 (2-126)	9 (2-45)	< 0.001*
- Breast milk as initial enteral feeding, n (%)	184 (92)	99 (91)	0.831
- Fortified breast milk, n (%)	198 (99)	102 (94)	0.019*
- Mean of max PF concentration, kcal/oz ($\pm$ SD)	24 ($\pm$ 2)	24 ($\pm$ 1)	0.002*
- Mean of maximum enteral feeding total volume, mL/kg/day ($\pm$ SD)	156 ($\pm$ 10)	154 ($\pm$ 8)	0.251
- Mean of maximum calories, kcal/kg/day ($\pm$ SD)	128 ($\pm$ 8)	123 ($\pm$ 8)	0.891
Medication treatment			
- Post- natal steroid use, n (%)	33 (16)	6 (6)	0.060
- Diuretic drug, n (%)	35 (17)	6 (6)	0.030*
- Aminophylline, n (%)	118 (59)	65 (60)	0.874
- Median initial multivitamin, day (range)	11 (3-127)	10 (5-45)	0.003*
- Median initial iron supplement, day (range)	19 (10-140)	18 (12-52)	< 0.001*
Co-morbidities			
- RDS with surfactant, n (%)	57 (28)	36 (33)	0.392
- PDA with treatment, n (%)	72 (36)	35 (32)	0.512
- NEC, n (%)	44 (22)	8 (7)	0.001*
- Severe IVH (gr 3-4), n (%)	9 (4)	5 (5)	0.965
- BPD, n (%)	70 (35)	32 (29)	0.328
- ROP, n (%)	55 (27)	22 (20)	0.162
- Proven sepsis, n (%)	20 (10)	3 (3)	0.021*
Outcomes			
Median length of stay, day (range)	55 (16-381)	45 (7-223)	< 0.001*
Median cost, Thai baht (range)	294,833 (48,722-2,584,449)	209,079 (24,494-2,339,900)	0.001*

*Statistically significant

PROM, premature rupture of membranes; TPN, total parenteral nutrition; PF, preterm formula; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity

longer hospital stays (55 [16-381] vs 45 [7-223] days, $p < 0.001$) and higher hospital costs (294,833 [48,722-2,584,449] vs 209,079 [24,494-2,339,900] THB, $p < 0.001$) than non-EUGR infants. The significant risk factors were subsequently calculated for odds ratio, 95%CI, and p -value, as presented in Table 2.

Multivariate analysis was conducted to control for several potential confounders, as demonstrated in Table 3. The significant risk factors found to increase the risk of EUGR among infants with GA less than 32 weeks or VLBW included definite NEC (OR 2.45, 95%CI 1.004-5.98, $p = 0.049$), maternal gestational hypertension (adjusted OR 2.78, 95%CI 1.46-5.32, $p = 0.002$), and multiple births (adjusted OR 2.29, 95%CI 1.23-4.23, $p = 0.008$).

DISCUSSION

In this study, the incidence of EUGR was 64.8% in infants with GA less than 32 weeks or VLBW, which aligns with previous studies, particularly those from China, Taiwan, Spain, and Italy (1, 5, 6, 8, 9, 24). In contrast, the EUGR incidence in our study was significantly higher than in US studies (7). All 76 SGA infants were identified with EUGR (100%).

Liao (1) and Figueras-Aloy (9) found that multiple births were a risk factor for EUGR, which is consistent with our study (adjusted OR = 2.29, 95%CI 1.24-4.24). Maternal gestational hyperten-

sion was also significantly associated with EUGR (adjusted OR = 2.79, 95%CI 1.46-5.33), a finding supported by Za Zhi and Figueras-Aloy. Both factors were also associated with intrauterine growth restriction (IUGR), as found in our study.

Definite NEC was a significant risk factor for EUGR (adjusted OR = 2.45, 95%CI 1.00-5.99) because NEC causes bowel inflammation and a longer duration of NPO time. This finding is similar to those of Clark (7) and Figueras-Aloy (9). From this finding, the prevention of NEC should be more emphasized, including nutritional issues, feeding protocols for preterm infants, and reducing the prolonged use of antibiotics.

In our study, infants who received oral diuretics for more than two weeks (adjusted OR = 2.62, 95%CI 0.99-6.98, $p = 0.05$) with doses of 1-3 mg/kg/day of furosemide, spironolactone, or hydrochlorothiazide due to chronic conditions, including 74% with moderate to severe BPD and others with acyanotic congenital heart disease with increased pulmonary blood flow, were found to be significant risk factors for EUGR. Although the use of diuretics was found to be not statistically significant after further analysis, it may still impact growth outcomes. Prolonged use of diuretics, particularly loop diuretics like furosemide, can negatively affect growth outcomes. Diuretics increase the excretion of essential electrolytes

Table 2. Univariate logistic analysis of factors associated with EUGR

Risk factors	Odds ratio	95% confidence interval	p-value
Proven sepsis, n (%)	3.90	1.13-13.45	0.031
Diuretic drug, n (%)	3.61	1.47-8.90	0.005
NEC, n (%)	3.53	1.60-7.82	0.002
Maternal gestational hypertension, n (%)	2.35	1.27-4.34	0.006
Multiple births, n (%)	1.84	1.04-3.27	0.035
Mean of initial parenteral glucose, mg/kg/min ($\pm$ SD)	1.28	1.10-1.48	0.001
Mean of max PF concentration, kcal/oz ($\pm$ SD)	1.26	1.04-1.52	0.016
Median time to full enteral feeding, day (range)	1.07	1.02-1.12	0.001

NEC, necrotizing enterocolitis; EUGR, extrauterine growth restriction

Table 3. Multivariate logistic regression analysis of factors associated with EUGR

Risk factors	Adjusted odds ratio	95% confidence interval	p-value
Maternal gestational hypertension, n (%)	2.78	1.46-5.32	0.002
NEC, n (%)	2.45	1.004-5.98	0.049
Multiple births, n (%)	2.29	1.23-4.23	0.008

NEC, necrotizing enterocolitis; EUGR, extrauterine growth restriction

and nutrients, such as sodium, potassium, calcium, and chloride, which are critical for growth and development in preterm infants (25). Chronic diuretic therapy may lead to imbalances in these electrolytes and contribute to poor weight gain and linear growth, potentially exacerbating the risk of EUGR (26). Since oral diuretics are frequently used in our hospital, adjusting the treatment strategy to reduce their use should be encouraged.

A strength of this study is that all medical records were thoroughly reviewed using proper data gathering methods, and a standardized definition for EUGR diagnosis was applied. However, the study is limited by its retrospective design, which introduces potential bias, particularly in the definition of certain risk factors. For example, NEC was only defined as definite NEC if it met stage II or III criteria by the modified Bell's staging, whereas NEC stage I, which involves NPO management for 1–3 days, could also affect infant growth but was not included. Similarly, in cases of PDA without medical or surgical management, fluid intake may have been restricted to treat the condition, potentially impacting growth and contributing to EUGR.

Additionally, this study used the Fenton growth curve to define EUGR in the Thai population. The Fenton growth curve was developed primarily from data on Western populations, which may not accurately reflect the growth patterns of Asian infants, including Thai infants, who typically have smaller birth weights and body sizes compared to Caucasian infants (14, 15). This discrepancy could lead to an overestimation of EUGR incidence in the Thai population. Furthermore, as the Fenton curve is based on intrauterine growth patterns, it may not fully account for postnatal growth in preterm infants, especially those with complex medical conditions (16). This limitation underscores the need for population-specific growth references that better capture the growth trajectories of Thai infants as a means of improving the accuracy of EUGR diagnosis and management.

Based on our study findings, improving antenatal care to manage maternal conditions, such as gestational hypertension, and providing counseling on the risk of EUGR associated with multiple pregnancies are important. During hospitalization, special attention should be given to infants at

high risk of EUGR, particularly those classified as SGA. Careful monitoring of these infants, along with adjusting feeding strategies to ensure adequate energy intake and reduce complications like NEC, is essential. Additionally, minimizing the use of diuretics is crucial to promoting better growth outcomes in VLBW infants.

CONCLUSIONS

Multiple births, maternal gestational hypertension, SGA status, and NEC are associated with a higher risk of EUGR in very preterm or VLBW infants. Providing proper antenatal care for mothers with multiple pregnancies or gestational hypertension, along with optimized postnatal care, can help improve growth outcomes and reduce the incidence of EUGR in these infants.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contribution

N.R.: contributed to concept and design the study, acquisition and analysis of the data, draft the manuscript; M.P.: contributed to concept and design the study, analysis and interpretation of the data and critically revise the manuscript. All authors approved the final manuscript as submitted.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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