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Original Article

# Prevalence and factors associated with extrauterine growth restriction in premature infants

**Komang Tria Anggareni, I Gusti Lanang Sidiartha, I Wayan Dharma Artana, I Gusti Ngurah Made Suwarba, I Nyoman Budi Hartawan, I Wayan Gustawan**

## *Abstract*

***Background*** Extrauterine growth restriction (EUGR) is common in preterm infants and has been shown to affect their neurodevelopment. Significant variability exists in the criteria used to define EUGR and a standard definition has not yet been established. Several factors associated with EUGR have been identified, yet EUGR remains a problem in preterm infants. There is still much to be explored regarding risk factors associated with EUGR.

***Objective*** To determine the prevalence and factors associated with EUGR in preterm infants.

***Methods*** This cross-sectional study included randomly selected premature infants (<37 weeks gestational age) who were admitted to levels II and III Neonatal Ward at Prof. Dr. I.G.N.G. Ngoerah Hospital from May 2022 to August 2023.

***Results*** Of 185 subjects, the prevalence of EUGR in preterm infants was 47% and there were significant associations between EUGR and birth weight <1500 g (PR 8.814; 95%CI: 3.943 to 19.7; P=0.000), small for gestational age/SGA (PR 28.95; 95%CI: 3.79 to 220.1; P=0.000), neonatal sepsis (PR 4.29; 95%CI: 2.21 to 8.31; P=0.000), hyaline membrane disease/HMD (PR 2.12; 95%CI: 1.16 to 3.88; P=0.021), use of respiratory support (PR 2.57; 95%CI: 1.35 to 4.92; P=0.005), initiation of enteral nutrition at >48 hours (PR 2.23; 95%CI: 1.21 to 4.09; P=0.014) and length of stay/LOS >14 days (PR 8.11; 95%CI: 4.13 to 15.9; P=0.000). Multivariate analysis revealed birth weight <1500 g (aPR 5.14; 95%CI: 1.55 to 17.06; P=0.007), SGA (aPR 24.26; 95%CI: 2.64 to 222.6; P=0.005), presence of sepsis (aPR 2.35; 95%CI: 1.00 to 5.5; P=0.049), and length of hospital stay >14 days (aPR 4.93; 95%CI: 2.15 to 11.31; P=0.000) maintained positive significant associations with EUGR.

***Conclusion*** The prevalence of EUGR in preterm infants is 47%. Birth weight <1500 g, small for gestational age, sepsis, and length of stay >14 days are associated with EUGR in preterm infants. **[Paediatr Indones. 2024;64:405-11; DOI: https://doi.org/10.14238/pi64.5.2024.405-11** ].

***Keywords:*** *associated factors, EUGR, preterm, prevalence*

Premature birth, defined as delivery before 37 weeks of gestation, is a significant global health concern. Premature infants face numerous challenges as they transition from the protective uterine environment to the outside world. Complications arising from premature birth constitute a leading cause of mortality in children under five years of age, contributing to nearly one million deaths in 2015.[1] Gestational age and birth weight are two crucial factors for predicting an infant's prognosis. Low birth weight in preterm infants serves as a critical indicator of poor outcomes. Premature babies with small gestational age (SGA) have a 10-40 times greater risk of death in the first month of life compared to term babies with appropriate gestational age (AGA).[2] Thus, postnatal growth is critical to improving survival and reducing poor outcomes in premature babies.

Understanding the prevalence and factors associated with extrauterine growth restriction (EUGR) is essential for optimizing the care and outcomes of premature infants. EUGR represents

From the Department of Child Health, Medical Faculty of Universitas Udayana/Prof. dr. I G. N. G. Ngoerah Hospital, Denpasar, Bali, Indonesia.

**Corresponding author:** I Gusti Lanang Sidiartha. Department of Child Health, Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G Ngoerah Hospital. Bali, Indonesia. Email: lanang_sidiartha@unud.ac.id.

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the failure to achieve adequate extrauterine growth and is a common occurrence among premature infants.[3-5] Studies have revealed a high incidence of EUGR in premature infants.[6,7] Factors associated with EUGR include prematurity, low birth weight, younger gestational age, use of respiratory support, comorbidities (such as respiratory distress, sepsis, congenital anomalies, and necrotizing enterocolitis), and inadequate nutrition.[6-10]

Despite the identification of several factors linked to EUGR, it remains a concern in premature infants. Significant variability exists in the criteria for defining EUGR, and a standard definition has yet to be established. Additionally, there is no consensus on the best timing for assessment or the most effective growth monitoring tools. The debate continues over the appropriate terminology to describe inadequate postnatal growth. Moreover, studies on EUGR in Indonesia is still limited. Therefore, further investigation into the prevalence and factors associated with EUGR in premature infants is both relevant and imperative.

## Methods

The study design was a retrospective observational approach using a cross-sectional method. We explored risk factors, including birth weight <1500 g, gestational age <32 weeks, birth weight on gestational age based on the Lubchenco chart into SGA (under 10th percentile), AGA (between 10-90th percentile), and large gestational age (LGA) (above 90th percentile), comorbidities, respiratory support, enteral nutrition initiation, and length of stay (LOS). EUGR was the dependent variable. Data were collected in the Neonatal Care Unit at Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, from May 2022 to August 2023. From the 2022-2023 neonatal register data, a list of potentially eligible infants was generated based on the inclusion and exclusion criteria. Subsequently, a random sampling process was conducted to select the required number of subjects.

Inclusion criteria were premature infants born with a gestational age of less than 37 weeks, who had been admitted to the Neonatal Care Unit at Prof. Dr. I G.N.G. Ngoerah Hospital from May 2022 to August 2023, discharged for medical reasons with the approval of the attending physician, and had complete medical record data. Patients who died during treatment or underwent gastrointestinal surgery were excluded from this study.

The minimum required sample size was 185 subjects. Secondary data collected through medical records included subjects' characteristics and the variables under investigation (birth weight category based on gestational age, use of respiratory support, comorbidities, and initiation of enteral nutrition). *The Intergrowth 21st Curve* was used as a reference for determining EUGR.[11] All data were tabulated, entered, and coded according to their respective categories and further processed using *SPSS 25.0* software. Bivariate analysis was conducted by cross-tabulating to examine the relationship between these independent variables and the dependent variables. Multivariate analysis was carried out using logistic regression tests.

This study has obtained ethical clearance from the Research and Development Unit of Prof. Dr. I G.N.G. Ngoerah Hospital and approval from the Ministry of Health of the Republic of Indonesia, Directorate General of Health Effort Improvement.

## Results

Of 185 infants in the study, 51.9% were male. Most subjects were moderate and late preterm (75.7%) with birth weight >1500 g (73%), delivered by Caesarean section (67%), had adequate gestational age (AGA) (162; 87.6%), and the most common comorbidity was sepsis (118 cases; 63.8%). Most subjects had a length of hospital stay of less than 14 days (103; 55.7%). In our study, the prevalence of EUGR in premature infants was 47% (**Table 1**).

Factors such as birth weight, gestational age, SGA, sepsis, neonatal meningitis, neonatal pneumonia, NEC, HMD, hyperbilirubinemia, use of respiratory support, initiation of enteral nutrition >48 hours, and length of hospital stay >14 days were analyzed by Chi-square test **Table 2** shows that birth weight <1500 g (PR 8.814; 95% 3.943 to 19.7; P=0.000), SGA (PR 28.95; 95% 3.79 to 220.1; P=0.000), presence of sepsis (PR 4.29; 95% 2.21 to 8.31; P=0.000), HMD (PR 2.12; 95%CI 1.16 to 3.88; P=0.021), use of respiratory support (PR 2.57; 95%CI

**Table 1**. Characteristics of subjects

| Characteristics | (N=185) |
|---|---|
| Gender, n (%) | |
| Male | 96 (51.9) |
| Female | 89 (48.1) |
| Gestational age, n (%) | |
| <32 weeks | 454 (24.3) |
| >32 weeks | 140 (75.7) |
| Birth weight, n (%) | |
| <1500 g | 504 (27) |
| >1500 g | 135 (73) |
| Delivery mode, n (%) | |
| Caesarean section | 124 (67) |
| Vaginal | 61 (33) |
| LOS, n (%) | |
| <14 days | 103 (55.,7) |
| >14 days | 82 (44.,3) |
| Birth weight category based on gestational age, n (%) | |
| SGA | 21 (11.4) |
| AGA | 162 (87.6) |
| LGA | 2 (1.1) |
| Comorbidities, n (%) | |
| Sepsis | 118 (63.,8) |
| Meningitis | 20 (10.,8) |
| Pneumonia | 49 (26.,5) |
| NEC | 20 (10.,8) |
| Hyperbilirubinemia | 107 (57.,8) |
| HMD | 70 (37.,8) |
| Extrauterine growth, n(%) | |
| EUGR | 87 (47) |
| Not EUGR | 98 (53) |

NEC=necrotizing enterocoitis; HMD=hyaline membrane disease

1.35 to 4.92; P=0.005), initiation of enteral nutrition at >48 hours (PR 2.23; 95%CI 1.21 to 4.09; P=0.014) and LOS>14 days (PR 8.11; 95%CI 4.13 to 15.9; P=0.000) were significantly associated with EUGR

Multivariate analysis with logistic regression revealed that only birth weight <1500 g (aPR 5.14; 95%CI 1.55 to 17.06; P=0.007), SGA (aPR 24.26; 95%CI 2.64 to 222.6; P=0.005), presence of sepsis (aPR 2.35; 95%CI 1.00 to 5.5; P=0.049), and length of hospital stay >14 days (aPR 4.93; 95%CI 2.15 to 11.31; P=0.000) were significantly and positively associated with the occurrence of EUGR (**Table 3**). All variables examined in this study collectively influenced EUGR to the extent of 45.6% (r2 0.456).

## Discussion

We noted a considerably high prevalence of EUGR among premature infants, with approximately 47% of infants affected. The absence of a consensus defining EUGR in a standardized manner makes it difficult to compare this result with previous studies. In addition to varying definitions of EUGR among studies, differing incidence EUGR rates can also be attributed to the use of different growth curves, namely *Fenton, INeS,* and *Intergrowth-21st*.[11] A study compared EUGR prevalences using several different curves and found a lower EUGR prevalence with the *Intergrowth-21st* curve compared to the *Fenton* and *INeS* curves.[11]

One of the key takeaways from our study is that EUGR is a complex issue with multiple contributing factors. We found that gestational age, birth weight, length of hospital stays, and the

**Table 2**. Chi-square bBivariate analysis of the association between EUGR and risk factors

| Variables | EUGR | | PR (95%CI) | P value* |
|---|---|---|---|---|
| | Yes (n=87) | No (n=98) | | |
| Birth weight | | | 8.814 (3.943-19.7) | 0.000 |
| <1500 gram | 41 (82) | 9 (18) | | |
| >1500 gram | 46 (34.1) | 89 (65.9) | | |
| Gestational age | | | 2.0 (1.009-3.963) | 0.067 |
| <32 weeks | 27 (60) | 18 (40) | | |
| >32 weeks | 60 (42.9) | 80 (57.1) | | |
| Birth weight category based on gestational age | | | 28.95 (3.79-220.1) | 0.000 |
| SGA | 20 (95.2) | 1 (4.8) | | |
| No SGA | 67 (40.9) | 97 (59.1) | | |
| Neonatal sepsis | | | 4.29 (2.21-8.31) | 0.000 |
| Yes | 70 (59.3) | 48 (40.7) | | |
| No | 17 (25.4) | 50 (74.6) | | |
| Neonatal meningitis | | | 2.94 (1.07-8.03) | 0.052 |
| Yes | 14 (70) | 6 (30) | | |
| No | 73 (44.2) | 92 (55.8) | | |
| Neonatal pneumonia | | | 1.39 (0.72-2.68) | 0.412 |
| Yes | 26 (53.1) | 23 (46.9) | | |
| No | 61 (44.9) | 75 (55.1) | | |
| NEC | | | 1.43 (0.56-3.64) | 0.604 |
| Yes | 11 (55) | 9 (45) | | |
| No | 76 (46.1) | 89 (53.9) | | |
| Hyperbilirubinemia | | | 1.16 (0.65-2.09) | 0.725 |
| Yes | 52 (48.6) | 55 (51.4) | | |
| No | 35 (44.9) | 43 (55.1) | | |
| HMD | | | 2.12 (1.16-3.88) | 0.021 |
| Yes | 41 (58.6) | 29.0 (41.4) | | |
| No | 46 (40.0) | 69.0 (60.0) | | |
| Oxygenation support | | | 2.57 (1.35-4.92) | 0.006 |
| Yes | 68 (54,4) | 57 (45.6) | | |
| No | 19 (31.7) | 41 (68.3) | | |
| Initiation of enteral feeding | | | 2.23 (1.21-4.09) | 0.014 |
| >48 hours | 41 (59.4) | 28 (40.6) | | |
| <48 hours | 46 (39.7) | 70 (60.3) | | |
| LoS | | | 8.11 (4.13-15.9) | 0.000 |
| >14 days | 70 (68) | 33 (32) | | |
| <14 days | 17 (20.7) | 64 (79.3) | | |

*Chi-square test

presence of comorbidities such as neonatal sepsis were significantly associated with EUGR. This multifactorial nature of EUGR highlights the need for a comprehensive and multidisciplinary approach to neonatal care.

Gestational age and birth weight are well-established factors influencing infant growth and development. Premature infants, by definition, are born before completing a full-term gestation, which places them at a higher risk of growth restriction. Our findings emphasize the importance of monitoring these parameters closely and tailoring interventions to the specific needs of infants with lower gestational age and birth weight to mitigate the risk of EUGR. Birth weight has been shown to have a significant relationship with EUGR. A previous study found a 2.2-fold increased risk of EUGR in infants with a birth weight <1,500 grams.[6] Low birth weight babies are more likely to have medical conditions that contribute to EUGR, such as respiratory problems, heart defects, and infections. These conditions can make it difficult for the baby to grow and develop as

**Table 3**. Multivariate analysis of the association between infant factors and EUGR and risk factors

| Variables | Adjusted PR Exp (B) | 95%CI | P value |
|---|---|---|---|
| Birthweight <1500 | 5.14 | 1.55-17.06 | 0.007 |
| Gestational age <32 weeks | 0.36 | 0.12-1.12 | 0.078 |
| SGA | 24.26 | 2.64-222.6 | 0.005 |
| Neonatal sepsis | 2.35 | 1.00-5.5 | 0.049 |
| Neonatal meningitis | 1.61 | 0.51-5.05 | 0.415 |
| Pneumonia | 0.77 | 0.28-2.14 | 0.614 |
| NEC | 0.57 | 0.17-1.91 | 0.364 |
| Hyperbilirubinemia | 0.99 | 0.46-2.18 | 0.998 |
| HMD | 1.46 | 0.65-3.27 | 0.358 |
| Oxygenation support | 0.59 | 0.19-1.89 | 0.377 |
| Initiation of enteral feeding >48 hours | 0.79 | 0.34-1.87 | 0.596 |
| LOS >14 days | 4.93 | 2.15-11.31 | 0.000 |

expected. Environmental factors that contribute to EUGR, such as economic problems, malnutrition, and lack of access to health services have also been associated with low birth weight.[8,12]

Gestational age and EUGR were not significantly associated with our subjects. In contrast, a previous study found that prematurity was a risk factor for EUGR, with a similar mechanism to that of low birth weight babies.[10] Our results could have been because premature babies receive more aggressive management and attention compared to babies with more mature gestational age. These results are also in accordance with the strong relationship between SGA and EUGR in this study, where the older gestational age combined with lower birth weight is linked to a higher risk of EUGR.

We also analyzed several comorbid factors and EUGR, but only sepsis showed a significant association by multivariate analysis. The presence of comorbidities, such as neonatal sepsis, shows the complexity of EUGR. This finding was similar to previous study which found that late-onset neonatal sepsis increased the risk of EUGR by 4.9 times.[13] In addition, another study found a significant association between sepsis and body weight below the 10$^{th}$ percentile at the corrected age of 36 weeks (OR 2.2).[14] Infection triggers inflammation that increases metabolic demands and, due to unstable conditions, led clinicians to consider limiting enteral nutrition intake.[15]

The relationship between sepsis and EUGR remains unclear as to whether postnatal growth failure can make the baby vulnerable to serious infections leading to sepsis, or vice versa. However, a study on subjects who had been matched based on birth weight, found a significant negative relationship between sepsis and postnatal growth three weeks after the onset of sepsis; this persisted for at least two months after the diagnosis of sepsis. This study even found an increased risk of growth failure in subjects who experienced recurrent episodes of sepsis.[16]

Unlike sepsis, meningitis, and NEC, as other infectious comorbidities often experienced by premature babies, did not show a significant relationships to EUGR in our study. This could have been because there were too few cases of NEC and meningitis in our subjects to determine a relationship with EUGR. It may be necessary to categorize NEC cases that may be more at risk of being associated with EUGR based on the degree of NEC. Infants with additional health challenges may be more susceptible to growth restriction. This finding highlights the need for a comprehensive approach to neonatal care that not only addresses EUGR directly but also manages and prevents comorbidities to promote healthy growth.

The consequences of prematurity and comorbidities experienced have an impact on the length of hospital stay. We found that a length of stay >14 days was significantly associated with EUGR. Previous study using a cut-off of 21 days also found that the risk of EUGR increased by 2.7 times with

longer lengths of stay.[6] Another study in China found that the duration of hospitalization was significantly longer in the EUGR group (26.5 days) than in the non-EUGR group (16.5 days).[17] In the first two weeks of life, newborns experience a physiological weight loss due to loss of fluids and loss of fat stores of around 10% of body weight at birth. This weight loss phenomenon is not reflected on growth charts, so all babies appear to experience growth failure where there is a decrease of half to one percentile line during the first two weeks.[18] However, in our study, physiological weight loss did not have an impact on EUGR in the first two weeks of life, EUGR increased with the length of treatment, so premature babies with a length of stay >14 days required earlier intervention with nutritional therapy to prevent EUGR.

Nutritional factors are part of neonatal care, which greatly determines the success of catch-up growth in premature babies. Nutritional goals during the early days should strive to prevent catabolism typically seen during the postnatal transition following preterm birth. However, we did not find a relationship between early initiation of enteral nutrition and EUGR.[19] Further research needs to be carried out to explore other nutritional factors that may be related to EUGR, such as the duration to reach full feed, total protein intake in the first eight days, total caloric intake in the first 15 days, and duration of use of parenteral nutrition.[20]

In conclusion, the prevalence of EUGR in premature infants treated at Prof. Dr. I.G.N.G. Ngoerah Hospital is 47%. Growth failure is a multifactorial process consisting of patient factors, comorbidities, and nutritional interventions/intake. In our study, notable findings were host factors (lower birth weight, SGA), comorbidities (sepsis), and neonatal care (length of stay >14 days), that are significantly associated with EUGR in premature infants. However, further research needs to be carried out to explore other nutritional factors that may be related to EUGR.

## Conflict of interest

None declared.

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