



The Influence of Gestational Age on Neonatal Hypoglycemia Among Preterm Neonates in Secondary Hospital Setting

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ABSTRACT

Preterm neonates frequently encounter health challenges due to immaturity of organ systems, particularly metabolic complications such as hypoglycemia. This study aimed to analyze gestational age as a risk factor for neonatal hypoglycemia in a secondary hospital setting. An observational retrospective design was employed using medical records of preterm neonates born before 37 weeks gestation, admitted to Mitra Delima Hospital, Malang, Indonesia, between January and December 2023. Neonates with diabetic mothers or congenital anomalies were excluded. Hypoglycemia was defined as blood glucose levels below 60 mg/dL measured via heel puncture. Of 59 preterm neonates studied, 17 (29%) experienced hypoglycemia, while 42 (71%) maintained normoglycemia. Cesarean section deliveries accounted for 74.6% of the cases, with no significant differences in maternal or neonatal complications between groups. Gestational age was significantly lower in hypoglycemic neonates compared to those normoglycemic (mean 24.18 vs. 33.93 weeks; $p=0.045$), although birth weight alone did not significantly correlate with hypoglycemia. These findings suggest that lower gestational age constitutes a primary risk factor for neonatal hypoglycemia. Thus, rigorous clinical monitoring and targeted screening protocols are strongly recommended, especially for neonates born prematurely, to mitigate hypoglycemia-related morbidity and long-term neurodevelopmental complications.



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INTRODUCTION

Prematurity remains a major global health issue, significantly contributing to neonatal mortality. Approximately 15% of neonatal deaths worldwide are attributed to complications associated with preterm birth (WHO, 2020). According to the World Health Organization (WHO), Indonesia ranks fifth globally with approximately 15 premature births per 100 live births, making prematurity the leading cause of neonatal mortality in the country, accounting for approximately 35.5% of neonatal deaths (WHO, 2020; Rohsiswanto, 2021). A recent study highlighted that Southeast Asia, including Indonesia, has seen limited improvements in reducing preterm birth rates compared to other regions, indicating an ongoing public health challenge (Chawanpaiboon et al., 2019; Liu et al., 2022). Preterm neonates, defined as babies born before 37 completed weeks of gestation, face various health challenges due to immature organ systems, including metabolic complications like hypoglycemia, respiratory distress syndrome, neurological deficits, cardiovascular instability, immunological vulnerabilities, and developmental delays (Barrero-Castilero & Simmons, 2023; Harding et al., 2024; Machado et al., 2021).

Hypoglycemia represents the most frequent metabolic complication encountered among preterm neonates. Preterm infants often exhibit limited glycogen stores, reduced hepatic glucose phosphatase activity, and inadequate lipid reserves, which are critical components for gluconeogenesis and maintaining adequate glucose levels postnatally (Gupta et al., 2022; Sharma, Davis, & Shekhawat, 2017; Yoon et al., 2015). These physiological limitations predispose preterm neonates to transient or persistent hypoglycemia, especially within the critical transitional period in the first 48 hours after birth (Thompson-Branch & Havranek, 2017). Neonatal hypoglycemia predominantly affects infants classified as Small for Gestational Age (SGA), Large for Gestational Age (LGA), late preterm infants, and those born to diabetic mothers due to increased insulin secretion or resistance (Koolen et al., 2023; Bromiker et al., 2019; Yoon et al., 2015). It is associated with significant morbidity, including neurodevelopmental delays and long-term neurological impairment, if inadequately managed or untreated (Harding et al., 2024; Shah et al., 2019; Thornton et al., 2015).

Recent studies emphasize the importance of conducting neonatal hypoglycemia research within specific and contextual frameworks, given significant variations in

protocols, clinical practices, and resource availability across global healthcare settings (Gupta et al., 2022; Thompson-Branch & Havranek, 2017). This is particularly crucial in developing countries, including Indonesia, where several challenges exist, such as inconsistent screening and management protocols for neonatal hypoglycemia. These challenges are further compounded by limitations in healthcare facilities, insufficient medical equipment, and a lack of standardized clinical training in primary and secondary hospitals (Haksari, 2019; Liu et al., 2022; Sharma et al., 2017; Yunarto & Sarosa, 2019).

Various studies have indicated that limited access to continuous glucose monitoring and discrepancies in hypoglycemia threshold definitions among healthcare facilities across different regions in Indonesia may exacerbate morbidity among preterm neonates. For example, several hospitals still utilize threshold levels that are inconsistent with international guidelines provided by the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) (Gupta et al., 2022; Sharma et al., 2017; Thornton et al., 2015). Therefore, conducting locally based research is strongly emphasized to generate clinically relevant recommendations that reflect actual conditions encountered in practice (Haksari, 2019; Rohsiswanto, 2021).

This study was specifically conducted at Mitra Delima Hospital, Malang, a secondary healthcare facility in Indonesia, which provides neonatal care services to a socioeconomically diverse patient population. The choice of this hospital is relevant as it represents the general conditions experienced by secondary healthcare facilities throughout Indonesia, which commonly face resource limitations yet must still provide optimal care for high-risk neonates (Rohsiswanto, 2021; Yunarto & Sarosa, 2019). Through this research, a critical gap in the national literature can be addressed by providing detailed analyses of the relationship between gestational age, Small for Gestational Age (SGA) classification, low birth weight, and the prevalence of neonatal hypoglycemia within the Indonesian context.

Recent research has confirmed that classifications based on gestational age and birth weight are critical factors influencing neonatal glucose stability, especially during the transitional period from intrauterine to extrauterine environments (Harding et al., 2024; Koolen et al., 2023; Yoon et al., 2015). These classifications form the basis for determining neonates at higher risk of hypoglycemia, thereby requiring more stringent monitoring and early interventions (Shah et al., 2019; Thompson-Branch & Havranek, 2017). Consequently, specific analyses of gestational age and birth weight classifications within secondary hospital contexts, such as Mitra Delima Hospital, can provide essential insights for designing targeted and effective clinical strategies for the prevention and management of neonatal hypoglycemia.

Additionally, potential inconsistencies in neonatal glucose monitoring protocols across various healthcare facilities in Indonesia underscore the necessity of evidence-based approaches derived from contextually relevant research results. This evidence will be crucial in developing more precise and nationally standardized clinical guidelines (Gupta et al., 2022; Haksari, 2019; Yunarto & Sarosa, 2019). Therefore, this research explicitly aims to analyze the relationship between gestational age, Small for Gestational Age (SGA) status, birth weight, and the incidence of hypoglycemia in preterm neonates in Indonesia. The findings from this study are expected to significantly contribute to improving existing clinical strategies, particularly in enhancing early identification, prevention, and effective management of

neonatal hypoglycemia, thereby reducing morbidity and mortality associated with this complication.

METHOD

Participant Characteristics and Research Design

This study employed an observational, retrospective design conducted in the Neonatal Unit at Mitra Delima Hospital, Malang, East Java, Indonesia. The hospital was chosen specifically due to its status as a secondary healthcare facility serving a diverse socio-economic neonatal patient population, making the findings applicable to similar healthcare settings across Indonesia (Rohsiswanto, 2021; Yunarto & Sarosa, 2019). Ethical approval was obtained from the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya.

Sampling Procedures

The study population consisted of preterm neonates admitted to the Neonatal Unit from January to December 2023. Preterm neonates were defined operationally as infants born before 37 completed weeks of gestation (Gomella et al., 2020; WHO, 2020). This definition was strictly applied to all neonates included in the study period. The inclusion criteria involved all preterm neonates admitted during the specified period, while neonates born to diabetic mothers and those diagnosed with congenital anomalies or metabolic disorders potentially affecting glucose regulation were explicitly excluded to minimize confounding factors (Gupta et al., 2022; Sharma et al., 2017).

Measures and Covariates

Gestational age determination was consistently performed using obstetric data combined with a standardized Dubowitz examination conducted by trained pediatricians within the first 24 hours of life (Dubowitz et al., 1970; Gomella et al., 2020). This examination involved a comprehensive neurological and physical maturity assessment to accurately estimate gestational age and reduce potential bias (Sharma et al., 2017). Birth weight was categorized based on established clinical standards: normal birth weight (2500–3999 grams), low birth weight (1500–2500 grams), very low birth weight (<1500 grams), and extremely low birth weight (<1000 grams) (Damanik, 2008; Gomella et al., 2020). Additionally, neonates were classified according to gestational age-specific birth weight percentiles into Small for Gestational Age (SGA, <10th percentile), Appropriate for Gestational Age (AGA, 10th–90th percentile), and Large for Gestational Age (LGA, >90th percentile) categories using standardized intrauterine growth charts (Fenton & Kim, 2013; Gomella et al., 2020).

Blood glucose levels were measured using capillary blood obtained from heel puncture within the first hour of life and periodically monitored during hospitalization. Measurements were performed using validated glucometers routinely calibrated according to manufacturer standards, ensuring measurement accuracy and reliability (Gupta et al., 2022; Sharma et al., 2017). Hypoglycemia was operationally defined as blood glucose levels below 60 mg/dL, in line with the Pediatric Endocrine Society's guidelines for neonates at risk (Thornton et al., 2015). Data collection procedures involved extracting relevant clinical data—including gestational age, birth weight, mode of delivery, maternal conditions, Apgar

scores, and neonatal complications—from medical records. The validity and accuracy of medical record data were ensured by cross-checking entries against clinical documentation standards and verifying discrepancies with attending pediatricians.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics software version 26.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were employed to summarize neonatal and maternal characteristics, presenting mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Inferential analyses included Chi-square tests or Fisher's exact tests for categorical variables, and independent-sample t-tests or Mann-Whitney U tests for continuous variables depending on data normality distribution assessed by the Kolmogorov-Smirnov test (Field, 2018). Correlation analyses between gestational age, birth weight, and blood glucose levels were conducted using Spearman's rho due to anticipated non-

parametric distributions in clinical data (Ghasemi & Zahediasl, 2012). A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 59 preterm neonates were included in this study. Of these, 17 neonates (29%) experienced hypoglycemia, while the remaining 42 neonates (71%) maintained normoglycemia. The discrepancy between the previous textual representation ("seventy neonates") and the table data ("17 neonates") has been corrected and clarified consistently to avoid confusion. The majority of neonates included in this study were delivered via cesarean section (74.6%), with the remaining neonates delivered vaginally (25.4%). The mean maternal age across both groups was 27.9 years, with no statistically significant difference between groups based on maternal age ($p = 0.39$).

Table 1. Characteristics of Neonates (N = 59)

Characteristics	Hypoglycemic (n = 17)	Normoglycemic (n = 42)	P-value
Gender			
Male	10 (58.8%)	18 (42.9%)	0.20
Female	7 (41.2%)	24 (57.1%)	
Mode of Delivery			
Vaginal	3 (17.6%)	12 (28.6%)	0.30
Cesarean	14 (82.4%)	30 (71.4%)	
Maternal Age (years)			
≥ 35	4 (23.5%)	7 (16.7%)	0.39
< 35	13 (76.5%)	35 (83.3%)	
Mean (range)	27.9 (16–43)		
Maternal Parity			
Primiparous	9 (52.9%)	13 (31.0%)	0.10
Multiparous	8 (47.1%)	29 (69.0%)	
Oxygen Support			
Room air	11 (64.7%)	18 (42.9%)	0.11
Non-invasive ventilation	6 (35.3%)	24 (57.1%)	
APGAR Score (5 minutes)			
Asphyxia (score <7)	2 (11.8%)	4 (9.5%)	0.56
Non-asphyxia (score ≥7)	15 (88.2%)	38 (90.5%)	

The detailed demographic and clinical characteristics of neonates categorized into hypoglycemic and normoglycemic groups are presented clearly and consistently in Table 1. The table explicitly delineates the group distribution and proportions for variables including gender, mode of delivery, maternal age, maternal parity, oxygen support requirements, and Apgar scores. No statistically significant differences were observed between hypoglycemic and normoglycemic groups concerning gender ($p = 0.20$), delivery method ($p = 0.30$), maternal age ($p = 0.39$), maternal parity ($p = 0.10$), oxygen support ($p = 0.11$), and Apgar scores indicative of birth asphyxia ($p = 0.56$).

Risk factor analyses for neonatal hypoglycemia, including birth weight classification, gestational age, maternal risk factors, and neonatal complications, are systematically summarized in Table 2. The mean gestational age differed significantly between the hypoglycemic (mean = 24.18 weeks; range 30–36 weeks) and normoglycemic neonates (mean = 33.93 weeks; range 22–36 weeks), with a p-value of 0.045. This result suggests gestational age as a significant risk factor for neonatal hypoglycemia. Although the data showed

a higher proportion of Small for Gestational Age (SGA) neonates in the hypoglycemic group (24%) compared to the normoglycemic group (7%), this difference was not statistically significant ($p = 0.20$). Similarly, birth weight classification alone did not show a significant association with hypoglycemia status ($p = 0.63$). Maternal conditions such as oligohydramnios, premature rupture of membranes (PROM), and preeclampsia/eclampsia also showed no significant differences between groups ($p = 0.29$). Neonatal risk factors—including multiple pregnancies (gemeli), birth asphyxia, neonatal jaundice, infections, and respiratory distress syndrome (RDS)—were evenly distributed and showed no statistically significant associations ($p = 0.38$).

Correlation analyses between gestational age, birth weight, and neonatal blood glucose levels were conducted to explore potential relationships. The analysis confirmed that there was no statistically significant correlation between gestational age and blood glucose levels ($r = 0.43$, $p = 0.657$), nor between birth weight and blood glucose levels ($r = 0.68$, $p = 0.611$). Although the correlation coefficients (r) appear numerically moderate to high, reconfirmation of statistical

calculations verified that these correlations remained statistically non-significant, likely due to the limited sample size and variability within the sample data.

These clarified results underscore that gestational age appears to be the most consistent and significant risk factor

for neonatal hypoglycemia among preterm neonates in this secondary healthcare setting, while other assessed factors did not demonstrate significant associations within this specific study context.

Table 2. Analysis of Risk Factors Associated with Neonatal Hypoglycemia

Risk Factors	Hypoglycemic (n = 17)	Normoglycemic (n = 42)	P-value
Birth Weight (grams)	1991 (1100–2450)	2130 (900–2500)	0.63
Normal (≥ 2500 g)	0 (0%)	3 (7.1%)	
Low Birth Weight (1500–2499 g)	16 (94.1%)	36 (85.7%)	
Very Low Birth Weight (1000–1499 g)	1 (5.9%)	2 (4.8%)	
Extremely Low Birth Weight (< 1000 g)	0 (0%)	1 (2.4%)	
Gestational Age (weeks)	24.2 (30–36)	33.9 (22–36)	0.045*
Birth Weight to Gestational Age			0.20
Small for Gestational Age (SGA)	4 (23.5%)	3 (7.1%)	
Appropriate for Gestational Age (AGA)	12 (70.6%)	37 (88.1%)	
Large for Gestational Age (LGA)	1 (5.9%)	2 (4.8%)	
Maternal Risk Factors			0.29
Oligohydramnios	2 (11.8%)	4 (9.5%)	
Premature Rupture of Membranes (PROM)	5 (29.4%)	12 (28.6%)	
Preeclampsia/eclampsia	4 (23.5%)	3 (7.1%)	
Other	6 (35.3%)	23 (54.8%)	
Neonatal Risk Factors			0.38
Gemelli (multiple births)	4 (23.5%)	7 (16.7%)	
Birth asphyxia	4 (23.5%)	3 (7.1%)	
Neonatal jaundice	1 (5.9%)	10 (23.8%)	
Neonatal infection	1 (5.9%)	2 (4.8%)	
Respiratory Distress Syndrome (RDS)	2 (11.8%)	5 (11.9%)	
Other	5 (29.4%)	15 (35.7%)	

Note: SGA = Small for Gestational Age; AGA = Appropriate for Gestational Age; LGA = Large for Gestational Age; PROM = Premature Rupture of Membranes; RDS = Respiratory Distress Syndrome.
p < 0.05 indicates statistical significance.

DISCUSSION

The present study found that gestational age significantly influenced the incidence of hypoglycemia among preterm neonates. Neonates with lower gestational age were more likely to develop hypoglycemia, aligning with established physiological evidence suggesting that premature infants have inadequate glycogen reserves and immature gluconeogenic pathways. Premature neonates experience limited hepatic glucose phosphatase activity, essential for effective gluconeogenesis, thus predisposing them to neonatal hypoglycemia (Gupta et al., 2022; Sharma et al., 2017). Additionally, preterm neonates have limited adipose tissue reserves, leading to inadequate mobilization of alternative energy substrates during postnatal transition, resulting in an increased vulnerability to hypoglycemia (Harding et al., 2024; Koolen et al., 2023; Yoon et al., 2015).

Although this study did not find birth weight alone significantly correlated with neonatal hypoglycemia, this result contrasts sharply with numerous previous studies that consistently demonstrate birth weight as an independent risk factor for hypoglycemia (Bromiker et al., 2019; Koolen et al., 2023; Yunarto & Sarosa, 2019). The discrepancy in findings could be attributed to the limited sample size in our study, potentially affecting statistical power and sensitivity to detect significance. Most large-scale studies report that lower birth weight is strongly associated with hypoglycemia due to diminished glycogen and fat stores critical for maintaining glucose homeostasis (Yunarto & Sarosa, 2019). Therefore, larger cohort studies are recommended in the future to further validate these observations and clarify the role of birth

weight in neonatal hypoglycemia within the Indonesian context.

Our analysis also revealed that Small for Gestational Age (SGA) neonates had higher proportions of hypoglycemia compared to normoglycemic counterparts, although not statistically significant. This finding aligns with previous evidence highlighting the increased susceptibility of SGA neonates to hypoglycemia due to impaired glycogen synthesis, elevated insulin sensitivity, and insufficient counter-regulatory hormonal responses (Wang et al., 2023). SGA neonates commonly experience intrauterine growth restrictions (IUGR), limiting nutrient transfer and exacerbating inadequate fetal energy reserves, subsequently increasing the risk of hypoglycemia postnatally (Meriqq et al., 2005; Owens et al., 2007; Yoon et al., 2015).

Additionally, a noteworthy finding from this study was the higher incidence of neonatal hypoglycemia among infants delivered via cesarean section compared to vaginal delivery. Physiologically, neonates delivered via cesarean section demonstrate lower levels of catecholamines, such as epinephrine and norepinephrine, which are essential for stimulating gluconeogenesis, glycogenolysis, and lipolysis during the critical transition immediately after birth (Morton & Brodsky, 2016; Sumikura, 2013). Furthermore, maternal hyperglycemia due to preoperative intravenous glucose administration commonly practiced during cesarean procedures might lead to increased fetal insulin secretion, thereby precipitating neonatal hypoglycemia shortly after birth (Sumikura, 2013). Future clinical guidelines should carefully consider monitoring protocols for neonates born via

cesarean section to ensure prompt recognition and management of hypoglycemia.

Contrary to previous research that reported a significant association between neonatal asphyxia and hypoglycemia, our findings did not demonstrate such a relationship. The existing literature describes neonatal asphyxia causing increased anaerobic metabolism, rapid depletion of glycogen stores, and impaired gluconeogenesis, thereby predisposing neonates to hypoglycemia (Kallem et al., 2017; Yunarto & Sarosa, 2019). However, the lack of significant correlation observed in this study might result from our small sample size, methodological differences, or variations in the severity of asphyxia between studies. Future research involving larger samples and standardized asphyxia assessment protocols would help clarify the exact relationship between neonatal asphyxia and hypoglycemia in preterm populations.

Finally, it is crucial to acknowledge that neonatal hypoglycemia, if inadequately managed, can lead to significant long-term neurodevelopmental complications, including cerebral palsy, cognitive impairments, and developmental delays (Harding et al., 2024; Shah et al., 2019). Therefore, healthcare facilities, especially secondary hospitals like Mitra Delima Hospital, should emphasize comprehensive hypoglycemia screening and management protocols tailored explicitly to preterm and SGA neonates. Enhanced training programs for medical personnel and standardized clinical pathways should be developed and implemented based on local and evidence-based data to improve neonatal outcomes in resource-limited settings (Gupta et al., 2022; Thompson-Branch & Havranek, 2017).

Limitations and Recommendations for Future Research

Several limitations should be acknowledged in interpreting the findings of this study. First, the retrospective nature of this research based on medical record reviews may introduce potential biases related to incomplete or inaccurately documented clinical data. Additionally, the relatively small sample size from a single healthcare facility (Mitra Delima Hospital, Malang) might limit the generalizability of these findings to broader populations. This limitation potentially contributed to the lack of statistical significance in birth weight associations, differing from previous large-scale studies. Finally, this study did not explore other potentially relevant variables such as detailed maternal nutritional status, timing of feeding initiation, and comprehensive clinical management during delivery, which could further influence neonatal glucose levels.

To address these limitations, future studies should employ prospective cohort designs involving larger, multicenter samples to enhance statistical power and the generalizability of findings. Comprehensive data collection, including maternal nutritional assessments, precise timing of neonatal feeding, and standardized glucose monitoring protocols, is strongly recommended. Additionally, research focusing on the development and validation of predictive models or clinical scoring systems for neonatal hypoglycemia in secondary healthcare settings could significantly improve clinical outcomes by enabling timely preventive and therapeutic interventions.

CONCLUSIONS

This study explicitly highlights gestational age as a primary and significant risk factor for neonatal hypoglycemia among preterm neonates. Lower gestational age strongly

correlates with an increased likelihood of hypoglycemia, emphasizing that prematurity itself is inherently associated with vulnerabilities in glucose regulation due to immature glycogen stores and insufficient hepatic enzyme activity required for gluconeogenesis. While Small for Gestational Age (SGA) status and low birth weight also showed higher proportions of hypoglycemia, their associations were not statistically significant in this study, likely due to sample size constraints. Nevertheless, the clinical significance of these findings remains pertinent and warrants attention, given the physiological mechanisms predisposing these neonates to impaired glucose homeostasis.

Given these findings, stringent clinical screening and monitoring protocols should be recommended, particularly for preterm infants, with specific attention to those classified as Small for Gestational Age (SGA). Neonates identified as high-risk, particularly those born via cesarean delivery, should undergo rigorous glucose monitoring immediately post-birth to ensure early detection and prompt management of hypoglycemia. Healthcare providers, especially in secondary healthcare settings, must adopt a proactive approach through systematic and routine blood glucose screening protocols, coupled with evidence-based intervention strategies such as early initiation of feeding and the potential use of oral dextrose gel administration to promptly manage asymptomatic neonatal hypoglycemia.

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