The incidence of and risk factors for hyperglycemia and hypoglycemia in preterm infants receiving early-aggressive parenteral nutrition

Angelika, Dina; Etika, Risa; Utomo, Martono Tri; Ladydi, Loysa; Sampurna, Mahendra Tri Arif; Handayani, Kartika Darma; Ugrasena, I. Dewa Gede; Sauer, Pieter JJ.

Published in:
Heliyon

DOI:
10.1016/j.heliyon.2023.e18966

Publication date:
2023

Heliyon 9 (2023) e18966

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

The incidence of and risk factors for hyperglycemia and hypoglycemia in preterm infants receiving early-aggressive parenteral nutrition

Dina Angelika [a], Risa Etika [a], Martono Tri Utomo [a,*], Loysa Ladydi [b], Mahendra Tri Arif Sampurna [c], Kartika Darma Handayani [a], I Dewa Gede Ugrasena [a], Pieter JJ. Sauer [d]

[a] Department of Pediatrics, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia
[b] Department of Pediatrics, Bakti Timah Hospital, Pangkalpinang, Bangka Belitung, Indonesia
[c] Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia
[d] Department of Pediatrics, University of Groningen, Beatrix Children's Hospital/UMCG, Groningen, Netherlands

ARTICLE INFO

Keywords:
Newborn
Risk factors
Premature-infant
Glucose
Prospective studies

ABSTRACT

Introduction: Optimizing nutritional support helps prevent extra uterine growth restriction and adverse long-term outcomes in preterm infants.
Objectives: This study aimed to analyze the incidence of and risk factors for hyperglycemia and hypoglycemia in preterm infants receiving early-aggressive parenteral nutrition (PN).
Methods: This prospective observational study included preterm infants receiving PN at the Neonatal Intensive Care Unit of Dr. Soetomo General Hospital between April 2018 and May 2019. Potential risk factors analyzed included asphyxia, sepsis, respiratory distress syndrome, multiple congenital anomalies, mortality, necrotizing enterocolitis, retinopathy of prematurity, the postoperative period, inotropic administration, glucose infusion rate (GIR) > 10–12 mg/kg/min, GIR 4–<5.5 mg/kg/min, and increase in GIR <1 mg/kg/min.
Results: Of the 105 preterm infants included, hyperglycemia and hypoglycemia were found in 14 (13.3%) and 26 (24.8%) infants, respectively, with most incidents occurring in the first week (hyperglycemia: 85.7%; hypoglycemia: 88.5%). Sepsis was an independent risk factor for hyperglycemia (odds ratio [OR]: 8.743, 95% confidence interval [CI]: 2.392–31.959; $P = 0.001$). Hypoglycemia independent risk factors included the postoperative period (OR: 4.425, 95% CI: 1.218–16.073; $P = 0.024$) and use of GIR 4–<5.5 mg/kg/min (OR: 2.950, 95% CI: 1.035–8.405; $P = 0.043$).
Conclusion: Hyperglycemia and hypoglycemia can occur in preterm infants receiving early-aggressive PN; most cases occur within the first week of life. Hypoglycemia correlated with low glucose intake, and hyperglycemia correlated with sepsis. Monitoring blood glucose levels in preterm infants receiving PN, especially in the first weeks of life, may decrease morbidity associated with hyperglycemia or hypoglycemia.

* Corresponding author. Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, St. Mayjen. Prof. Dr. Moestopo 47, Surabaya, 60132, Indonesia.
E-mail address: martono-t-u@fk.unair.ac.id (M.T. Utomo).

https://doi.org/10.1016/j.heliyon.2023.e18966
Received 4 January 2023; Received in revised form 11 July 2023; Accepted 3 August 2023
Available online 4 August 2023

1. Introduction

Optimizing nutritional support is crucial for preventing extra uterine growth restriction (EUGR) in preterm infants [1,2]. Nutritional deficits, particularly in protein and energy intake, during this critical period can contribute to EUGR and adversely impact neurodevelopment [3], growth [4], respiratory disorders [5], metabolic diseases [6], and visual/hearing ability in the long-term [7].

Abbreviations

PN	Parenteral Nutrition
GIR	Glucose Infusion Rate
NICU	Neonatal Intensive Care Unit
EUGR	Extra Uterine Growth Restriction
RDS	Respiratory Distress Syndrome
NEC	Necrotizing Enterocolitis
ROP	Retinopathy of Prematurity
BG	Blood Glucose
SD	Standard Deviation
OR	Odds Ratio
CI	Confidence Interval

Evidence-based guidelines now recommend the parenteral nutrition (PN) strategy, referred to as early-aggressive PN (the provision of protein and energy at a higher concentration than that of conventional PN) [2,8]. This PN practice should be started immediately after birth to achieve safe plasma glucose levels and improve energy balance [9,10]. Early-aggressive PN strategies pose a risk of hyperglycemia and hypoglycemia; however, the extent to which the incidence of hyperglycemia and hypoglycemia occurs in early-aggressive PN strategies is still a matter of debate [11,12]. Some studies recommended the administration of higher glucose levels to obtain greater calories [2], but another study found that giving lower glucose levels reduces morbidity [13]. Most of these studies are conducted in NICU'S in developed countries. In preterm infants, hyperglycemia and hypoglycemia have been positively correlated with mortality [12] and morbidities, like necrotizing enterocolitis (NEC) [14], bronchopulmonary dysplasia [15], retinopathy of prematurity (ROP) [16], intraventricular hemorrhage [17], neurodevelopmental disorders [18], cerebral injury [19], and respiratory distress syndrome (RDS) [20].

According to our hospital's protocol, we started administering amino acids, lipids, and dextrose solutions to the infants on the first day of life. We previously started with low doses of all three major nutrients to avoid metabolic complications; however, since 2012, our protocol changed to administering higher doses of amino acid, lipid, and glucose earlier. Administration early-aggressive PN strategies for preterm infants in developing countries are challenging nutritional practices. Therefore, this study aimed to analyze blood glucose (BG) levels in preterm infants receiving this early-aggressive PN and to identify risk factors for hyperglycemia and hypoglycemia.

2. Materials and methods

2.1. Study design and eligible participants

This was a prospective observational study. All preterm infants admitted to the Neonatal Intensive Care Unit (NICU) of Dr. Soetomo General Hospital, Surabaya, Indonesia between April 2018 and May 2019 and receiving PN were enrolled in this study. The inclusion criteria for this study were all preterm infants born at our hospital who required parenteral nutrition. Indications for parenteral nutrition according to the protocol at our hospital are infants who will not be on full enteral feeding within a period of five days. Infants born outside the hospital were excluded from this study. Informed consent was obtained from the infants' guardians. The study was approved by the Ethical Committee in Health Research at the Dr. Soetomo General Hospital, Surabaya, Indonesia (Reference number: 0203/KEPK/IV/2018). We also excluded infants who received steroids and/or methylxanthine [20,21], infants whose parents did not provide consent, and infants who were withdrawn from the study by their parents.

The sample size was calculated based on the formulation from Hulley et al. [22] with the following formula: an expected proportion of 0.5, a desired total width of 0.2, and a confidence interval (CI) of 95%; therefore, the calculation result was 96 samples. We expanded to 105 samples.

2.2. Parenteral and enteral nutrition protocol

All infants received PN according to the standard protocol in our NICU. PN was provided initially with a 4 Fr polyvinyl chloride umbilical catheter (Vygon, Ecouen, France) and then with a 1 Fr/28 G central venous polyurethane catheter inserted peripherally (Premicath; Vygon, Ecouen, France). The location of the catheters was confirmed by radiography. Since 2012, our NICU has been using

an all-in-one PN solution (all nutrients were placed in one container) [23] and no complications have been reported associated with this system.

Intravenous amino acids were administered on the first day with a dose of 2 g/kg/day and increased daily by 0.5 g/kg/day up to 3.5 g/kg/day [24]. Intravenous infusion of dextrose was administered with a GIR of at least 4 mg/kg/min and a maximum GIR of 12 mg/kg/min [25]. Lipids were administered starting with a dose of 1 g/kg/day and increased daily by 0.5 g/kg/day up to 3 g/kg/day [26] Several electrolytes and vitamins were added to the PN solution [2,8]. The total volume of fluid was started at 80 mL/kg/day, then increased daily by 10 mL/kg/day for the first 3 days and further increased by 20 mL/kg/day daily until the target volume of 180 mL/kg/day was achieved. Enteral nutrition was given on the first day of life at a dose of 10 mL/kg/day. If the infant tolerated this amount, then the volume was increased by 20 mL/kg/day. Infants received breast milk or preterm formula milk if breast milk was not available. PN was stopped when the enteral volume reached 120 mL/kg/day. All infants were monitored until PN was stopped and/or the infant died [1]. Table 1 describes the formulation of PN in our NICU.

2.3. Sampling of blood glucose levels

BG levels were monitored from the first day of PN administration starting immediately at birth. What is immediately after birth, then the glucose level of the infant is the level of the mother. BG levels were monitored 3 times daily for 2 days, then once daily until the infants no longer required PN. If hyperglycemia or hypoglycemia occurred, BG was measured 3 times daily until BG returned to be normal, after which the measurements were performed once daily until the infant no longer required PN. Hyperglycemia was defined as a BG level >150 mg/dL and hypoglycemia was defined as the BG level <45 mg/dL [11]. BG levels were measured from heel prick capillary blood samples (Terumo Medisafe EX, Tokyo, Japan). If the results of the BG level were inconclusive, the BG level was confirmed by a venous whole blood sample (Dimension EXL 200 by Siemens, Erlangen-Forchheim, Germany). Based on BG levels, we divided the infants into three groups: hyperglycemia, hypoglycemia, and normoglycemia.

2.4. Management of hyperglycemia and hypoglycemia

According to our protocol, the maximum GIR was 12 mg/kg/min. If BG levels >150 mg/dL, we reduced GIR by 0.5–2 mg/kg/min until BG levels returned to be normal. We did not use insulin as a routine therapy for neonatal hyperglycemia. If the infant was found to be hypoglycemia, then the glucose level infusion rate was increased by 0.5–2 mg/kg/day until the glucose level was normal. If the blood glucose level was normal in 2 consecutive examinations, then the monitoring of blood glucose levels was reduced to once per day. In cases of persistent hypoglycemia, the infant would be referred to the pediatric endocrine department [27,28].

2.5. Clinical variables

We recorded clinical variables including sex, gestational age, birth weight, BG level, mode of delivery, antenatal consultation (mothers who consulted with doctors or midwives during the antenatal period), maternal history, mortality, asphyxia, sepsis, RDS, multiple congenital anomalies, NEC, ROP, postoperative period, inotropic administration, the use of GIR 4–<5.5 mg/kg/min, the use

Table 1
The formulation of the parenteral nutrition in our NICU.

Nutrient	Dosage	Preparations
Amino acids	Administered on the first day with a dose of 2 g/kg/day and increased daily by 0.5 g/kg/day up to 3.5 g/kg/day [24]	Aminosteril Infant, Fresenius Kabi, Bad Homburg, Germany
Dextrose	Administered on the first day with a GIR of at least 4 mg/kg/min. If the infants tolerated that dosage, GIR was increased by 0.5–2 mg/kg/min per day, adjusted for daily fluid volume and BG level. The maximum GIR was 12 mg/kg/min [25]	Dextrose 10%; Satoria Aneka Industri, Surabaya, Jawa Timur
Lipids	Administered on the first day, starting with a dose of 1 g/kg/day and increased daily by 0.5 g/kg/day up to 3 g/kg/day [26]	Smoflipid 20%; Fresenius Kabi, Bad Homburg, Germany
Sodium	2–4 mmol/kg/day [2,8]	2.56 mmol/mL sodium chloride solution (sodium chloride 15%; Pharmaceutical Soetomo Hospital, Surabaya, Indonesia)
Potassium	1–2 mmol/kg/day [2,8]	1 mmol/mL potassium chloride solution (potassium chloride 7.46%; Otsuka Indonesia, Lawang, Indonesia)
Magnesium	0.1–0.3 mmol/kg/day [2,8]	0.8 mmol/mL magnesium-sulfate solution (magnesium sulfate 20%; Otsuka Indonesia, Lawang Indonesia)
Calcium	0.6–1.5 mmol/kg/day [2,8]	0.25 mmol/mL calcium gluconate solution (calcium gluconate 10%; Otsuka Indonesia, Lawang, Indonesia)
Phosphate	0.7 mmol/kg/day [2,8]	1 mmoL/mL sodium glycerophosphate solution (glycophos; Fresenius Kabi, Bad Homburg, Germany)
Water-soluble vitamins	1 mL/kg/day [2,8]	Soluvit® N; Fresenius Kabi, Bad Homburg, Germany
Fat-soluble vitamins	4 mL/kg/day [2,8]	Vitalipid® N; Fresenius Kabi, Bad Homburg, Germany

of GIR >10–12 mg/kg/min, and an increase in GIR <1 mg/kg/min.

Asphyxia was defined as an Apgar score at the 5 min of less than 5 [29]. Neonatal sepsis was defined asclinical manifestations of infection and a positive blood culture [30]. Respiratory distress syndrome (RDS) was defined by the presence of signs of respiratory distress and was supported by a typical radiographic appearance on chest radiography [31]. Necrotizing enterocolitis (NEC) was confirmed by the presence of gastrointestinal symptoms and supported by signs of pneumatosis intestinalis, pneumoperitoneum, or portal vein gas on abdominal radiographs [32]. Retinopathy of prematurity (ROP) was confirmed by indirect ophthalmoscopy [33].

2.6. Data and statistical analysis

Quantitative data are described using mean, range, and standard deviation (SD). Qualitative data are described using frequencies and percentages. Intergroup comparisons for categorical variables were analyzed using chi-square tests. To identify risk factors for the development of hyperglycemia and hypoglycemia, each candidate risk factor was initially analyzed by chi-square tests as a univariate model. Multivariate logistic regression analysis was then performed using a backward stepwise logistic regression model. Variables with a P value of $\leq$0.05 for odds ratio (OR) of 95% confidence interval (CI) using multivariate logistic regression analysis were accepted as independent risk factors. All statistical analyses were performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Characteristics of participants

A total of 124 infants met the inclusion criteria and were included in this study. Five infants were withdrawn, and 14 infants had

Table 2
Infant characteristics.

	n	%
Sex		
Male	53	50.5
Female	52	49.5
Gestational age		
<30 weeks	16	15.2
30–<34 weeks	35	33.3
34–<37 weeks	54	51.4
Birth weight		
<1000 g	17	16.2
1000–<1500 g	30	28.6
1500–<2000 g	40	38.1
2000–<2500 g	18	17.1
Mode of delivery		
Spontaneous	29	27.6
Caesarean section	76	72.4
Antenatal consultation		
Routine control	96	91.4
No routine control	9	8.6
Profile of blood glucose level		
Hyperglycemia	14	13.3
Hypoglycemia	26	24.8
Normoglycemia	65	61.9
Outcome		
Mortality	20	19
Survival	85	81
Maternal history		
Eclampsia	6	5.7
Severe pre-eclampsia	20	19.0
Chronic hypertension	6	5.7
Malignancy	3	2.9
Heart disorder	3	2.9
Diabetes mellitus	1	1.0
Hypothyroid	2	1.9
Asthma	1	1.0
HIV infection	3	2.9
Tuberculosis	2	1.9
Hepatitis	4	3.8
No previous disease history	54	51.4

Data are shown as number and percentage.
HIV, human immunodeficiency virus.

incomplete data; therefore, the data of 105 infants were analyzed. Of the 105 infants, 54 (51.4%) had a gestational age of 34–<37 weeks. The minimum birth weight was 600 g, and the maximum birth weight was 2400 g, with a mean of 1565 g and an SD of 443 g. Twenty (19.0%) mothers had severe pre-eclampsia, and 54 (51.4%) mothers did not have complications during pregnancy. Most infants (76 [72.4%]) were born by cesarean section and 96 (91.4%) were routinely controlled during the antenatal period. The characteristics of the 105 infants are shown in Table 2.

3.2. Incidence of hyperglycemia and hypoglycemia

Based on BG levels, we divided the infants into three groups: hyperglycemia, hypoglycemia, and normoglycemia. There were no significant differences in sex, gestational age, birth weight, mode of delivery, and antenatal consultation among the three groups. Twenty infants (19%) died in this study; there was no significant difference in mortality between the hyperglycemia, hypoglycemia, and normoglycemia groups. Hyperglycemia was observed in 14 (13.3%) infants and hypoglycemia in 26 (24.8%) infants. Twelve (85.7%) of the 14 hyperglycemia cases occurred in the first week, while the remaining two cases occurred in the second week. Twenty-three (88.5%) of the 26 hypoglycemia cases occurred in the first week, while the remaining three cases occurred in the second week. Characteristics of infants based on BG profiles are shown in Table 3. The mean of the 3 times daily BG measurement was 3 days (minimum 2 d, maximum 7 d, SD 1.7 d). The mean of the once daily BG measurement was 11 days (minimum 4 d, maximum 26 d, SD 5.3 d).

3.3. Factors associated with hyperglycemia and hypoglycemia

To identify risk factors for the development of hyperglycemia and hypoglycemia, we used univariate and multivariate logistic regression analysis models. The results of the univariate model are shown in Table 4 and those of the multivariate model in Table 5. Ten variables were analyzed as potential risk factors for the development of hyperglycemia, including asphyxia, sepsis, RDS, multiple congenital anomalies, mortality, NEC, ROP, postoperative period, inotropic administration, and the use of GIR >10–12 mg/kg/min. In the univariate analysis model, variables that significantly increased the risk of hyperglycemia were sepsis (OR = 6.390, 95% CI = 1.924–21.227; $P = 0.001$) and RDS (OR = 3.917, 95% CI = 1.024–14.975; $P = 0.035$). In the multivariate logistic regression analysis model, the independent risk factor for hyperglycemia was sepsis (OR = 8.743, 95% CI = 2.392–31.959; $P = 0.01$). The use of GIR >10–12 mg/kg/min did not increase the risk of hyperglycemia.

Eleven variables were analyzed for the development of hypoglycemia, including asphyxia, sepsis, RDS, multiple congenital anomalies, mortality, NEC, ROP, postoperative period, inotropic administration, the use of GIR 4–<5.5 mg/kg/min, and an increase in GIR <1 mg/kg/min. In the univariate analysis model, variables that significantly increased the risk of hypoglycemia were the postoperative period (OR = 4.482, 95% CI = 1.348–14.906; $P = 0.009$) and the use of GIR 4–<5.5 mg/kg/min (OR = 3.250, 95% CI = 1.180–8.953; $P = 0.019$). In the multivariate logistic regression analysis model, the independent risk factors for hypoglycemia were the postoperative period (OR = 4.425, 95% CI = 1.218–16.073; $P = 0.024$) and the use of GIR 4–<5.5 mg/kg/min (OR = 2.950, 95% CI = 1.035–8.405; $P = 0.043$). The increase in GIR to <1 mg/kg/min did not increase the risk of hypoglycemia.

Table 3
Characteristics of infants in the hyperglycemia, hypoglycemia, and normoglycemia groups.

	Hyperglycemia (n = 14)	Hypoglycemia (n = 26)	Normoglycemia (n = 65)	P[a]
	n (%)	n (%)	n (%)	
Sex				
Male	7 (50)	15 (57.7)	31 (47.7)	0.689
Female	7 (50)	11 (42.3)	34 (52.3)	
Gestational age				
<30 weeks	3 (21.4)	3 (11.5)	10 (15.4)	0.897
30–<34 weeks	4 (28.6)	8 (30.48	23 (35.4)	
34-<37 weeks	7 (50)	15 (57.7)	32 (49.2)	
Birth weight				
<1000 g	3 (21.4)	3 (11.5)	11 (16.9)	0.919
1000–<1500 g	3 (21.4)	7 (26.9)	20 (30.8)	
1500–<2000 g	6 (42.9)	12 (46.2)	22 (33.8)	
2000–<2500 g	2 (14.3)	4 (15.4)	12 (18.5)	
Mode of delivery				
Spontaneous	1 (7.1)	8 (30.8)	20 (30.8)	0.184
Caesarean section	13 (92.9)	18 (69.2)	45 (69.2)	
Antenatal consultation				
Routine control	12 (85.7)	24 (92.3)	60 (92.3)	0.714
No routine control	2 (14.3)	2 (7.7)	5 (7.7)	
Outcome				
Mortality	3 (21.4)	7 (26.9)	10 (15.4)	0.435
Survival	11 (78.6)	19 (73.1)	55 (84.6)	

Data are shown as number and percentage. $P \leq 0.05$ was considered significant.
[a] Chi-square test was used.

Table 4
Univariate risk factors for hyperglycemia and hypoglycemia.

Variable	n (%)	OR	95% CI	$P^{\ddagger}$
Hyperglycemia (n = 14)				
Asphyxia	2 (14.3)	3.625	0.598–21.963	0.138
Sepsis	9 (64.3)	6.390	1.924–21.227	0.001*
RDS	11 (78.6)	3.917	1.024–14.975	0.035*
Multiple congenital anomaly	0 (0)	1.110	1.037–1.188	0.218
Mortality	3 (21.4)	1.187	0.298–4.724	0.807
NEC	2 (14.3)	1.729	0.328–9.126	0.514
ROP	3 (21.4)	3.273	0.737–14.541	0.103
Post-operative period	3 (21.4)	2.209	0.526–9.284	0.270
Inotropic administration	4 (28.6)	2.909	0.777–10.887	0.101
GIR >10–12 mg/kg/min	3 (21.4)	1.500	0.371–6.070	0.568
Hypoglycemia (n = 26)				
Asphyxia	0 (0)	1.082	1.016–1.153	0.148
Sepsis	5 (19.2)	0.546	0.184–1.618	0.270
RDS	16 (61.5)	1.641	0.664–4.056	0.281
Multiple congenital anomaly	3 (11.5)	1.587	0.367–6.854	0.533
Mortality	7 (26.9)	1.711	0.604–4.846	0.309
NEC	4 (15.4)	2.212	0.572–8.550	0.241
ROP	3 (11.5)	1.342	0.321–5.615	0.687
Post-operative period	7 (26.9)	4.482	1.348–14.906	0.009*
Inotropic administration	4 (15.4)	1.124	0.325–3.889	0.854
GIR 4–<5.5 mg/kg/min	20 (76.9)	3.250	1.180–8.953	0.019*
Increase in GIR <1 mg/kg/min	22 (84.6)	1.991	0.614–6.458	0.245

Data are shown as number and percentage. ‡Chi-square test was used.
CI, confidence interval; GIR, glucose infusion rate; NEC, necrotizing enterocolitis; OR, odds ratio; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.
*$P \leq 0.05$.

Table 5
Multivariate logistic regression analysis for hyperglycemia and hypoglycemia.

Variable	OR	95% CI	*P*
Hyperglycemia			
Sepsis	8.743	2.392–31.959	0.001*
Hypoglycemia			
Post-operative period	4.425	1.218–16.073	0.024*
GIR 4–<5.5 mg/kg/min	2.950	1.035–8.405	0.043*

CI, confidence interval; GIR, glucose infusion rate; OR, odds ratio.
*$P \leq 0.05$.

4. Discussion

EUGR is a nutritional problem often observed in preterm infants. Preterm infants who experience EUGR are at risk for morbidities including bronchopulmonary dysplasia [5], ROP [7], NEC [34], intraventricular hemorrhage [17], and periventricular leukomalacia [7]. Long-term observations indicate that preterm EUGR infants have a risk of experiencing growth impairment, neurodevelopmental disorders, and impaired cognitive development that may affect future quality of life [35]. Improving nutritional strategies is beneficial for preventing EUGR in preterm infants [36]. Therefore, early-aggressive PN has been adopted as the standard of neonatal care in many countries [37].

Early-aggressive PN includes administration of high glucose doses, potentially increasing hyperglycemia risk [12,36]. The results of BG level monitoring during PN in this study showed that 13.3% of 14 infants experienced hyperglycemia, 76.9% of which occurred in the first week. Previous studies have shown wide variations in hyperglycemia incidence, ranging from 31.7% (19) to 80% [38]. Both increasing gestational age and birth weight are negatively correlated with the incidence of hyperglycemia [38]. Our study reported a lower hyperglycemia incidence (13.3%), most likely related to the relatively high gestational age of our infants (51.4% with gestational age 34–37 weeks). The early postnatal period is a critical phase for preterm infants, due to the interruption of the transplacental glucose supply after birth and abnormal glucose homeostasis, which causes a high risk of glucose imbalance disorders such as hyperglycemia or hypoglycemia [39,40].

In our study, 26 preterm infants receiving PN (24.8%) developed hypoglycemia, with most cases occurring in the first week of life, similar to the findings of a previous study [41]. Our results are similar to those of another study that reported a hypoglycemia incidence of approximately 30% in high-risk infants, including preterm, intra-uterine growth restriction, and small for gestational age infants [42]. Factors increasing hypoglycemia risk in preterm infants include smaller glycogen stores than term infants, exposure to perinatal stress, and maternal diabetes [43]. In this study, only one mother with diabetes mellitus was included, and the infant did not have

hypoglycemia.

To prevent hypoglycemia and meet the energy requirements needed for growth, it is recommended to start PN immediately after birth in preterm infants with a glucose intake ≥4–7 mg/kg/min, the basal glucose turnover rate for infants [40]. The infant is expected to remain normoglycemic with this GIR [44]. Infants receiving PN have a relatively low risk of developing hypoglycemia; however, inadequate glucose administration, no central venous access, or cyclic PN use increase vulnerability to hypoglycemia [11]. In this study, we found that a glucose intake <5.5 mg/kg/min significantly increased hypoglycemia risk. However, we also showed that increasing the GIR to <1 mg/kg/min did not significantly increase hypoglycemia risk. These findings are consistent with those of a previous study, which showed that gluconeogenesis remained unchanged despite a 60% reduction in GIR [45]. If the infant could tolerate the given GIR, then the GIR could be increased by 0.5–1 mg/kg/min up to 12–13 mg/kg/min [46]. However, a slow increase in GIR is better tolerated by preterm infants and minimizes the risk of hyperglycemia [47].

We found that the period after an operative intervention was a significant risk factor for hypoglycemia. Energy needs might be increased after a surgical procedure, but PN is often withheld due to potential complications that may arise [48]. Before and after gastrointestinal surgery, infants often require long-term PN due to non-optimal digestive function [49]. PN with a glucose intake of at least 6–8 mg/kg/min, preferably amino acids, must be given in the pre- and postoperative periods to achieve adequate glucose levels [50].

Hyperglycemia often occurs in preterm infants in the first week of life and is commonly caused by a high glucose intake, including the use of GIR >10 mg/kg/min [13]. According to our protocol, the maximum GIR is 12 mg/kg/min. If the infant was considered hyperglycemia (BG levels >150 mg/dL), we reduced GIR by 0.5–2 mg/kg/min until BG levels returned to be normal. We did not use insulin as a routine therapy in cases of neonatal hyperglycemia. We found that a GIR of 10–12 mg/kg/min did not increase hyperglycemia risk. Therefore, we conclude that a GIR up to 10–12 mg/kg/min is safe. We also studied whether hyperglycemia was related to factors other than high glucose intake. We determined that hyperglycemia was significantly related to sepsis and RDS, similar to the results of previous studies [20,38].

The use of amino acids and lipids can reduce hyperglycemia risk without increasing hypoglycemia risk, energy deficiency, and protein catabolism [51]. Barquetdeneb et al. [52] showed that amino acid administration within 4 h of birth can reduce hyperglycemia and hypoglycemia incidence in premature infants. Amino acid and lipid components are included as macronutrient components in our PN protocol. We administered amino acids and lipids in higher doses than conventional nutrition strategies and within the first 24 h of birth. Using amino acids and lipids reduces hyperglycemia and hypoglycemia risk in NICU infants.

This study found that asphyxia, ROP, and NEC were not related either to hyperglycemia or hypoglycemia in infants who received early aggressive NP. A meta-analysis study by Lei et al., in 2021 demonstrated that the relationship between ROP and hyperglycemia is not clear [33]. Kaempf et al. demonstrated that ROP was more common in infants with severe hyperglycemia with insulin administration [53]. This study also found that asphyxia was not associated with hypoglycemia. Other studies have demonstrated that perinatal asphyxia increases the risk of glucose dysregulation, therefore, the provision of an optimal nutritional strategy is required [54]. Our study found that NEC was not associated with either hyperglycemia or hypoglycemia. Other studies have similar results. Administration of oxygen is associated with ROP, in contrast to NEC [55]. In our study, oxygen requirements were not examined.

A limitation of this study is that our conclusions are based on BG measurements performed for clinical reasons, and not by strict protocol. Our hospital already has a parenteral nutrition protocol that contains the provision of both macronutrients and micronutrients for preterm infants based on evidence. However, in the clinical field, it is possible to provide therapy from a doctor based on clinical judgment. In addition, the number of monitoring blood glucose levels when hypoglycemia or hyperglycemia occurs which is 3 times per day is not enough so that the determination of cases of acute hypoglycemia or hyperglycemia may be missed. Monitoring glucose levels more often than 3 times a day is not feasible due to limited facilities and nurses at our hospital. Another limitation, we did not measure routinely glucose in urine or other components then glucose in blood. The results of glycosuria can vary over time and so cannot be used as a reliable indicator for assessing BG levels [56]. A hypoglycemia cannot be detected by analyzing urine. Further studies are required to analyze hyperglycemia and hypoglycemia incidence in extremely low birth weight infants; however, PN practices will continue to evolve. Moreover, longitudinal studies are needed to evaluate long-term impacts of hyperglycemia or hypoglycemia in preterm infants under such conditions.

In conclusion, beginning PN early at a high intake is important to prevent EUGR in preterm infants; however, early-aggressive PN strategies may increase hyperglycemia and hypoglycemia risk. We found a higher incidence of hypoglycemia than hyperglycemia in preterm infants receiving PN, and most incidences occurred in the first week of life. Hypoglycemia correlated with low glucose intake, while hyperglycemia correlated with sepsis. Monitoring BG levels in preterm infants receiving PN, especially in the first weeks of life, may decrease morbidity associated with hyperglycemia and hypoglycemia. Early-aggressive PN strategies in developing countries like our hospital are challenging nutritional practices. Therefore, this study can provide information about early-aggressive PN in developing countries or countries with limited facilities.

Author contribution statement

Conceived and designed the experiments; DA, PJJ, IDGU, MTU, and LL.
Performed the experiments; DA, LL, RE, MTA, KDH, and MTU.
Analyzed and interpreted the data; DA, LL, PJJ, MTA, and IDGU.
Contributed reagents, materials, analysis tools or data; MTU, RE, IDGU, DA, MTA, KDH, and LL.
Wrote the paper; All authors.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We wish to thank all staff in the Division of Neonatology and Pediatric Ward, the doctors, the nurses at the Dr. Soetomo General Academic Hospital, and Post-Graduate Doctoral Program Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia, for granting us permission and support for conducting this research. We would also like to thank Editage (www.editage.com) for English language editing.

References

[1] M. De Curtis, J. Rigo, The nutrition of preterm infants, (in eng), Early Hum. Dev. 88 (Suppl 1) (2012) S5–S7, https://doi.org/10.1016/j.earlhumdev.2011.12.020.
[2] N.D. Embleton, K. Simmer, Practice of parenteral nutrition in VLBW and ELBW infants, (in eng), World Rev. Nutr. Diet. 110 (2014) 177–189, https://doi.org/10.1159/000358466.
[3] H.C. Chien, C.H. Chen, T.M. Wang, Y.C. Hsu, M.C. Lin, Neurodevelopmental outcomes of infants with very low birth weights are associated with the severity of their extra-uterine growth retardation, Pediatr Neonatol 59 (2) (2018) 168–175, https://doi.org/10.1016/j.pedneo.2017.08.003 (in eng).
[4] V. Pampanini, et al., Preterm infants with severe extrauterine growth retardation (EUGR) are at high risk of growth impairment during childhood, (in eng), Eur. J. Pediatr. 174 (1) (2015) 33–41, https://doi.org/10.1007/s00431-014-2361-z.
[5] J. Figueras-Aloy, C. Palet-Trujols, I. Matas-Barceló, F. Botet-Mussons, X. Carbonell-Estrany, Extrauterine growth restriction in very preterm infant: etiology, diagnosis, and 2-year follow-up, (in eng), Eur. J. Pediatr. 179 (9) (2020) 1469–1479, https://doi.org/10.1007/s00431-020-03628-1.
[6] E. Castanys-Muñoz, et al., Systematic review indicates postnatal growth in term infants born small-for-gestational-age being associated with later neurocognitive and metabolic outcomes, (in eng), Acta Paediatr. 106 (8) (2017) 1230–1238, https://doi.org/10.1111/apa.13868.
[7] H. Nakanishi, H. Suenaga, A. Uchiyama, Y. Kono, S. Kusuda, Trends in the neurodevelopmental outcomes among preterm infants from 2003-2012: a retrospective cohort study in Japan, (in eng), J. Perinatol. 38 (7) (2018) 917–928, https://doi.org/10.1038/s41372-018-0061-7.
[8] D.H. Adamkin, P.G. Radmacher, Current trends and future challenges in neonatal parenteral nutrition, (in eng), J. Neonatal Perinat. Med. 7 (3) (2014) 157–164, https://doi.org/10.3233/npm-14814008.
[9] I. Guellec, et al., Biological impact of recent guidelines on parenteral nutrition in preterm infants, (in eng), J. Pediatr. Gastroenterol. Nutr. 61 (6) (2015) 605–609, https://doi.org/10.1097/mpg.0000000000000898.
[10] C.C. Hsiao, M.L. Tsai, C.C. Chen, H.C. Lin, Early optimal nutrition improves neurodevelopmental outcomes for very preterm infants, (in eng), Nutr. Rev. 72 (8) (2014) 532–540, https://doi.org/10.1111/nure.12110.
[11] D. Arsenault, , et al.A.S.P.E.N. Clinical, Guidelines: hyperglycemia and hypoglycemia in the neonate receiving parenteral nutrition, (in eng), JPEN - J. Parenter. Enter. Nutr. 36 (1) (2012) 81–95, https://doi.org/10.1177/0148607111418980.
[12] H.J. Stensvold, et al., Early enhanced parenteral nutrition, hyperglycemia, and death among extremely low-birth-weight infants, (in eng), JAMA Pediatr. 169 (11) (2015) 1003–1010, https://doi.org/10.1001/jamapediatrics.2015.1667.
[13] A.C. Tottman, et al., Relationships between early nutrition and blood glucose concentrations in very preterm infants, (in eng), J. Pediatr. Gastroenterol. Nutr. 66 (6) (2018) 960–966, https://doi.org/10.1097/mpg.0000000000001929.
[14] N.A. Mitchell, et al., Incidence and risk factors for hypoglycemia during fetal-to-neonatal transition in premature infants, (in eng), Front Pediatr 8 (2020) 34, https://doi.org/10.3389/fped.2020.00034.
[15] N.M. van der Lugt, V.E. Smits-Wintjens, P.H. van Zwieten, F.J. Walther, Short and long term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study, (in eng), BMC Pediatr. 10 (2010) 52, https://doi.org/10.1186/1471-2431-10-52.
[16] S. Mohamed, J.C. Murray, J.M. Dagle, T. Colaizy, Hyperglycemia as a risk factor for the development of retinopathy of prematurity, (in eng), BMC Pediatr. 13 (2013) 78, https://doi.org/10.1186/1471-2431-13-78.
[17] A. Auerbach, et al., Long duration of hyperglycemia in the first 96 hours of life is associated with severe intraventricular hemorrhage in preterm infants, (in eng), J. Pediatr. 163 (2) (2013) 388–393, https://doi.org/10.1016/j.jpeds.2013.01.051.
[18] G. Alexandrou, et al., Early hyperglycemia is a risk factor for death and white matter reduction in preterm infants, Pediatrics 125 (3) (2010) e584–e591, https://doi.org/10.1542/peds.2009-0449 (in eng).
[19] S. Chandran, V.S. Rajadurai, A.A.A. Haium, K. Hussain, Current perspectives on neonatal hypoglycemia, its management, and cerebral injury risk, Res. Rep. Neonatol. 5 (2015) 17–30, https://doi.org/10.2147/RRN.S55353.
[20] M.K. Sabzehei, S.A. Afjeh, M. Shakiba, P. Alizadeh, A.R. Shamshiri, F. Esmaili, Hyperglycemia in VLBW infants; incidence, risk factors and outcome, (in eng), Arch. Iran. Med. 17 (6) (2014) 429–434.
[21] P.J. Rozance, W.W. Hay Jr., Neonatal hyperglycemia, NeoReviews 11 (11) (2010) e632–e639, https://doi.org/10.1542/neo.11-11-e632.
[22] S.C. Hulley, S.R.W. Browner, D.N. Grady, TB, Designing Clinical Research, fourth ed., fourth ed., Lippincott Williams & Wilkins, Philadelphia, PA 19103 USA, 2013 ([Online]. Available).
[23] A.B. Blackmer, M.L. Partipilo, Three-in-one parenteral nutrition in neonates and pediatric patients: risks and benefits, (in eng), Nutr. Clin. Pract. 30 (3) (2015) 337–343, https://doi.org/10.1177/0884533615580596.
[24] M.Y. Liu, Y.Y. Chen, S.H. Hu, Y.K. Chen, S.J. Chang, The influence of aggressive parenteral nutrition to preterm and very low birth weight infants, Glob Pediatr Health 2 (2015), 2333794x14567192, https://doi.org/10.1177/2333794x14567192 (in eng).
[25] N.O. ElHassan, J.R. Kaiser, Parenteral nutrition in the neonatal intensive care unit, NeoReviews 12 (3) (2011) e130–e140, https://doi.org/10.1542/neo.12-3-e130.
[26] E. Tomsits, M. Pataki, A. Tölgyesi, G. Fekete, K. Rischak, L. Szollár, Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition, (in eng), J. Pediatr. Gastroenterol. Nutr. 51 (4) (2010) 514–521, https://doi.org/10.1097/MPG.0b013e3181de210c.
[27] A. Abramowski, R. Ward, A.H. Hamdan, Neonatal hypoglycemia, in: *StatPearls*Treasure Island (FL), StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC., 2023.
[28] D.H. Adamkin, Postnatal glucose homeostasis in late-preterm and term infants, (in eng), Pediatrics 127 (3) (2011) 575–579, https://doi.org/10.1542/peds.2010-3851.

[29] F.W. Sendeku, G.G. Azeze, S.L. Fenta, Perinatal asphyxia and its associated factors in Ethiopia: a systematic review and meta-analysis, (in eng), BMC Pediatr. 20 (1) (2020) 135, https://doi.org/10.1186/s12887-020-02039-3.
[30] I.H. Celik, M. Hanna, F.E. Canpolat, P. Mohan, Diagnosis of neonatal sepsis: the past, present and future, Pediatr. Res. 91 (2) (2022) 337–350, https://doi.org/10.1038/s41390-021-01696-z (in eng).
[31] F. Raimondi, et al., Lung ultrasound score progress in neonatal respiratory distress syndrome, Pediatrics 147 (4) (2021), https://doi.org/10.1542/peds.2020-030528 (in eng).
[32] R.M. Patel, J. Ferguson, S.J. McElroy, M. Khashu, M.S. Caplan, Defining necrotizing enterocolitis: current difficulties and future opportunities, Pediatr. Res. 88 (Suppl 1) (2020) 10–15, https://doi.org/10.1038/s41390-020-1074-4 (in eng).
[33] C. Lei, J. Duan, G. Ge, M. Zhang, Association between neonatal hyperglycemia and retinopathy of prematurity: a meta-analysis, (in eng), Eur. J. Pediatr. 180 (12) (2021) 3433–3442, https://doi.org/10.1007/s00431-021-04140-w.
[34] I.J. Griffin, D.J. Tancredi, E. Bertino, H.C. Lee, J. Profit, Postnatal growth failure in very low birthweight infants born between 2005 and 2012, (in eng), Arch. Dis. Child. Fetal Neonatal Ed. 101 (1) (2016) F50–F55, https://doi.org/10.1136/archdischild-2014-308095.
[35] S.M. Lee, N. Kim, R. Namgung, M. Park, K. Park, J. Jeon, Prediction of postnatal growth failure among very low birth weight infants, (in eng), Sci. Rep. 8 (1) (2018) 3729, https://doi.org/10.1038/s41598-018-21647-9.
[36] A. Dinerstein, R.M. Nieto, C.L. Solana, G.P. Perez, L.E. Otheguy, A.M. Larguia, Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants, (in eng), J. Perinatol. 26 (7) (2006) 436–442, https://doi.org/10.1038/sj.jp.7211539.
[37] S. Bolisetty, D. Osborn, J. Sinn, K. Lui, Standardised neonatal parenteral nutrition formulations - an Australasian group consensus 2012, BMC Pediatr. 14 (2014) 48, https://doi.org/10.1186/1471-2431-14-48 (in eng).
[38] K. Beardsall, et al., Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of the NIRTURE study, (in eng), J. Pediatr. 157 (5) (2010) 715–719, https://doi.org/10.1016/j.jpeds.2010.04.032, e1-3 doi:.
[39] D. Mitanchez, Glucose regulation in preterm newborn infants, (in eng), Horm. Res. 68 (6) (2007) 265–271, https://doi.org/10.1159/000104174.
[40] S.N. Taylor, J. Kiger, C. Finch, D. Bizal, Fluid, electrolytes, and nutrition: minutes matter, (in eng), Adv. Neonatal Care 10 (5) (2010) 248–255, https://doi.org/10.1097/ANC.0b013e3181f0823e.
[41] R. Bromiker, A. Perry, Y. Kasirer, S. Einav, G. Klinger, F. Levy-Khademi, Early neonatal hypoglycemia: incidence of and risk factors. A cohort study using universal point of care screening, (in eng), J. Matern. Fetal Neonatal Med. 32 (5) (2019) 786–792, https://doi.org/10.1080/14767058.2017.1391781.
[42] A. Sharma, A. Davis, P.S. Shekhawat, Hypoglycemia in the preterm neonate: etiopathogenesis, diagnosis, management and long-term outcomes, Transl. Pediatr. 6 (4) (2017) 335–348, https://doi.org/10.21037/tp.2017.10.06 (in eng).
[43] J. Stark, B. Simma, A. Blassnig-Ezeh, Incidence of hypoglycemia in newborn infants identified as at risk, (in eng), J. Matern. Fetal Neonatal Med. 33 (18) (2020) 3091–3096, https://doi.org/10.1080/14767058.2019.1568985.
[44] A.A. Van Kempen, et al., Adaptation of glucose production and gluconeogenesis to diminishing glucose infusion in preterm infants at varying gestational ages, (in eng), Pediatr. Res. 53 (4) (2003) 628–634, https://doi.org/10.1203/01.Pdr.0000054733.13366.Af.
[45] S.K. Chacko, J. Ordonez, P.J. Sauer, A.L. Sunehag, Gluconeogenesis is not regulated by either glucose or insulin in extremely low birth weight infants receiving total parenteral nutrition, (in eng), J. Pediatr. 158 (6) (2011) 891–896, https://doi.org/10.1016/j.jpeds.2010.12.040.
[46] S. Velaphi, Nutritional requirements and parenteral nutrition in preterm infants, S. Afr. J. Clin. Nutr. 24 (3) (2011) S27–S31, https://doi.org/10.1080/16070658.2011.11734377.
[47] P. Patel, J. Bhatia, Total parenteral nutrition for the very low birth weight infant, (in eng), Semin. Fetal Neonatal Med. 22 (1) (2017) 2–7, https://doi.org/10.1016/j.siny.2016.08.002.
[48] V. Westin, E. Stoltz Sjöström, F. Ahlsson, M. Domellöf, M. Norman, Perioperative nutrition in extremely preterm infants undergoing surgical treatment for patent ductus arteriosus is suboptimal, (in eng), Acta Paediatr. 103 (3) (2014) 282–288, https://doi.org/10.1111/apa.12497.
[49] J. Ayers, S.A. Graves, Perioperative management of total parenteral nutrition, glucose containing solutions, and intraoperative glucose monitoring in paediatric patients: a survey of clinical practice, Paediatr. Anaesth. 11 (1) (2001) 41–44, https://doi.org/10.1046/j.1460-9592.2001.00611.x (in eng).
[50] D.H. Teitelbaum, A.G. Coran, Perioperative nutritional support in pediatrics, Nutrition 14 (1) (1998) 130–142, https://doi.org/10.1016/s0899-9007(97)00229-3 (in eng).
[51] A. Mahaveer, C. Grime, C. Morgan, Increasing early protein intake is associated with a reduction in insulin-treated hyperglycemia in very preterm infants, (in eng), Nutr. Clin. Pract. 27 (3) (2012) 399–405, https://doi.org/10.1177/0884533612438730.
[52] M.L.-V. Morales- BarquetDeneb, B. Hernández-Pelaez, A.D.-F. Ortega-Vargas, D. Fernández-Carrocera, L.A. Echaniz-Aviles, OL., early parenteral protein and glucose control in extremely low birth weight infants, Acad J Ped Neonatol 4 (3) (2017), 555697, https://doi.org/10.19080/AJPN.2017.04.555697.
[53] J.W. Kaempf, A.J. Kaempf, Y. Wu, M. Stawarz, J. Niemeyer, G. Grunkemeier, Hyperglycemia, insulin and slower growth velocity may increase the risk of retinopathy of prematurity, (in eng), J. Perinatol. 31 (4) (2011) 251–257, https://doi.org/10.1038/jp.2010.152.
[54] E.F. Pinchefsky, J. Schneider, S. Basu, E.W.Y. Tam, C. Gale, Nutrition and management of glycemia in neonates with neonatal encephalopathy treated with hypothermia, (in eng), Semin. Fetal Neonatal Med. 26 (4) (2021), 101268, https://doi.org/10.1016/j.siny.2021.101268.
[55] O. Surmeli Onay, A. Korkmaz, S. Yigit, M. Yurdakok, Hypoxic-ischemic enterocolitis: a proposal of a new terminology for early NEC or NEC-like disease in preterm infants, a single-center prospective observational study, (in eng), Eur. J. Pediatr. 179 (4) (2020) 561–570, https://doi.org/10.1007/s00431-019-03539-w.
[56] M.C. Falcão, C.R. Leone, J.L. Ramos, Is glycosuria a reliable indicator of adequacy of glucose infusion rate in preterm infants?, (in eng), Sao Paulo Med. J. 117 (1) (1999) 19–24, https://doi.org/10.1590/s1516-31801999000100004.