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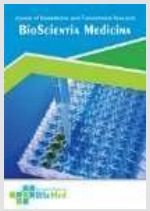

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Relationship between Hyperglycemia and Retinopathy of Prematurity in Very Low Birth Weight Infants: A Systematic Review

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A B S T R A C T

Background: Retinopathy of prematurity (ROP) is the major cause of neonatal blindness and may account for up to 10% of juvenile blindness. This systematic review evaluates the relationship between hyperglycemia and ROP in VLBW infants. **Methods:** PRISMA guidelines were used to conduct a systematic review using an online database: Google Scholar, PubMed, and the Wiley Online Library. Original research studies examining the association between hyperglycemia and ROP were the inclusion criteria. Animal studies, a letter to the editor, a commentary report, a review, a meta-analysis not available in full text in English or Bahasa Indonesia, and data in the study insufficient for analysis were all excluded. **Results:** This systematic review includes nine studies, six cohorts and three case-control studies, involving a total of 1,566 infants. Six studies indicated that newborns in the ROP group had lower mean gestational age and birthweight than those in the non-ROP group. Five investigations found that the mean glucose level in the ROP group was greater than in the non-ROP group. Six studies found that the prevalence of glycemia was much higher than in the non-ROP group. Eight of the nine studies found a significant relationship between hyperglycemia in VLBW infants, and only one found no significant relationship between them. The highest odds ratio and relative risk of hyperglycemia causing ROP were 14.27 (5.16–39.50); p-value <0.001 and 28.062 (7.881–99.924); p-value <0.001, respectively. The overall range of values found across the studies was also considered. **Conclusion:** Hyperglycemia has a significant relationship with ROP and is also a risk factor for ROP in VLBW infants.

1. Introduction

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy that affects premature infants and is the leading cause of blindness in children globally, particularly in middle-income countries such as India, China, and Indonesia.[1,2] The number of infants at risk for ROP has been increasing as premature births have increased, and survival rates have improved due to advances in neonatal care.[3] Globally, in 2010, it was estimated that 184,700 babies out of 14.9 million preterm babies developed ROP at any stage. Of these, 20,000 became blind or severely impaired (visual acuity between 20/200 and 20/400) due to ROP, and the remaining 12,300 developed mild to moderate visual impairment (between 20/40 and 20/200).[2,4,5]

Several risk factors have been linked to the development and progression of ROP. The two most powerful recognized risk factors for developing ROP are gestational age (GA) and birth weight (BW). Young gestational age is defined as less than 34 weeks, and particularly low birth weight newborns (1500 grams) are known to be at a higher risk of ROP. Previously, a high oxygen treatment concentration was thought to be the primary cause of ROP. However, ROP has been recorded in the absence of oxygen therapy.[2,6]

The pathogenesis of ROP is characterized by an anomaly in retinal vascular development controlled by

low insulin-like growth factor-1 (IGF-1) levels in the first phase and high levels of vascular endothelial growth factor (VEGF) in the second phase. Infants with low birth weight, especially those under 1000 g, experience hyperglycemia due to glucose intolerance. Neonates with birthweight under 1000 g are 18 times more likely than those over 2000 g to experience hyperglycemia.[7]

Hyperglycemia is a significant risk factor for preterm newborns for morbidity and mortality. Preterm newborns may experience a variety of physiological and biochemical processes that result in excessive glucose production, insulin resistance, or glucose intolerance; these metabolic abnormalities have wide-ranging consequences. Until now, several studies have been done to prove the relationship between hyperglycemia and ROP in preterm infants, especially very low birth weight infants.[8-12] Thus, this systematic review aims to gather information about the relationship between hyperglycemia and ROP in infants with very low birth weight.

2. Methods

Search strategy

We searched online journal databases for articles published up to July 2023. The research used three journal databases: Google Scholar, PubMed, and the Wiley Online Library. We used a Boolean operator with the terms "hyperglycemia" AND "retinopathy of prematurity" OR "ROP" AND "very low birth weight infants" to narrow down the search results. The timeframe for the search was limited to the past five years.

Study eligibility

Following the literature screening, the studies collected were evaluated for their eligibility criteria using a PRISMA diagram, as shown in Figure 1. The inappropriate or redundant study was removed. Following that, the abstract and full-text versions of the research were analyzed and scored based on the qualifying criteria. The inclusion criteria were as follows: (1) original research studies such as cohort, case-control, or cross-sectional studies evaluating the relationship or correlation between hyperglycemia and retinopathy of prematurity (ROP); (2) hyperglycemia defined as blood glucose level 150 mg/dL or 8.3 mmol/L; (3) study sample is low or very low birth weight infants defined as birthweight 2000 gram or 1500 gram; and (4) provided odds ratio (OR) or relative risk (RR). In comparison, the exclusion criteria were as follows: (1) animal studies, a letter to the editor, a commentary report, a review, and a meta-analysis; (2) studies not available in full text and not in English or Bahasa Indonesia; and (3) study with insufficient data for analysis.

Data gathering and selection

Two reviewers gathered data and selected studies that matched the eligibility conditions. The chosen research was then assessed independently based on the evidence and the study's quality assessment, and it was added for further investigation. All studies were thoroughly read to obtain the primary idea of the literature. Data extracted from the included study were first author, country of the study, year of publication, study design, sample and sample size, mean of birthweight (BW), mean of gestational age (GA), means of glucose level in case (ROP group) and control group (non-ROP group), the number of hyperglycemias in ROP and non-ROP group, and p-value of the relationship between hyperglycemia and ROP, OR or RR of hyperglycemia as a risk factor of ROP.

Study quality assessment

The Newcastle-Ottawa Scale (NOS) was used to measure study quality, which included three primary parameters: (1) selection, (2) comparability, and (3) outcomes. A maximum of four points are available for selection, two for comparability, and three for outcomes.[13] As a result, each study's maximum potential total points are nine. A study is considered qualified if it meets at least five criteria.

Data synthesis

The narrative synthesis incorporated all relevant papers on the association between hyperglycemia and ROP. This qualitative analysis examines the association between hyperglycemia and ROP in very low birth weight infants. A comprehensive narrative synthesis was performed to conclude the association between hyperglycemia and ROP in extremely low birth weight infants.

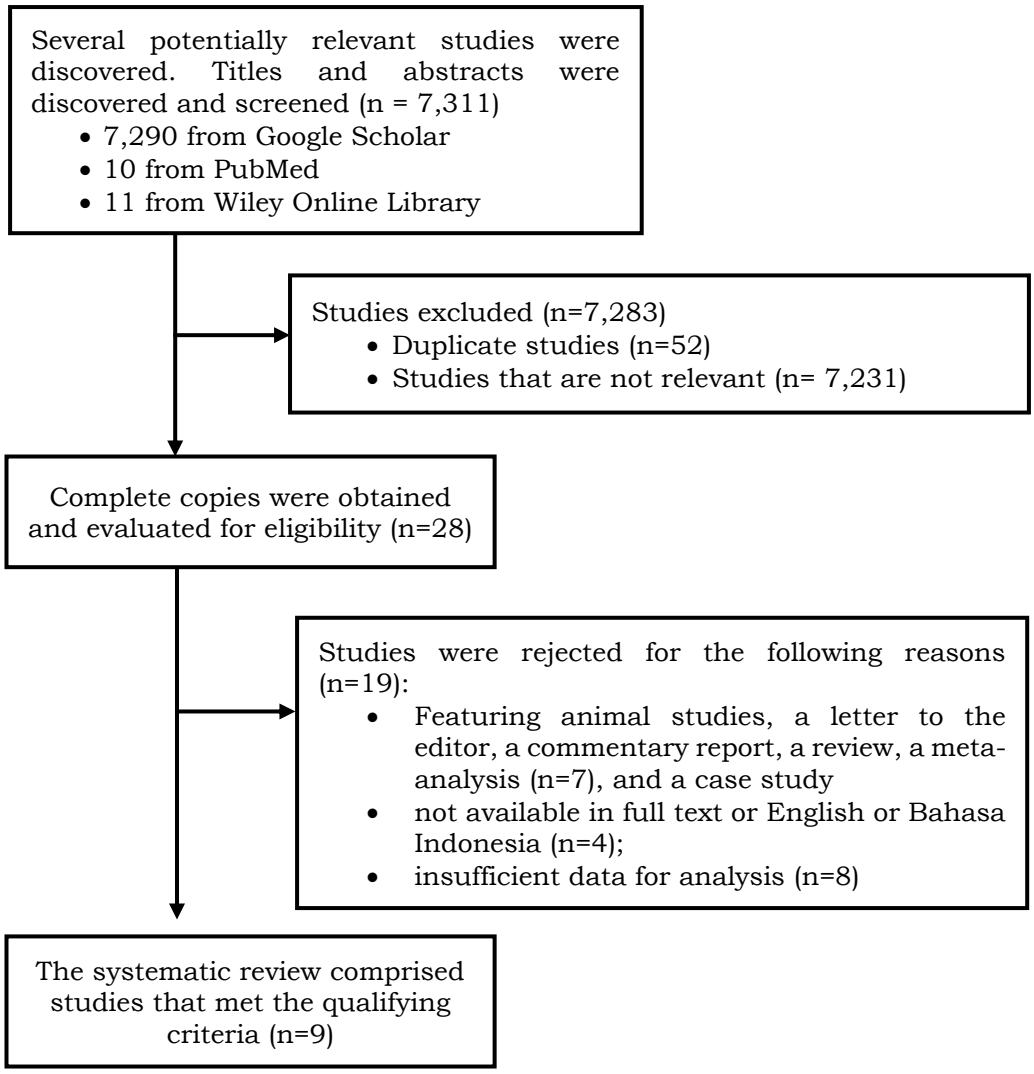

Figure 1. PRISMA diagram for systematic review.

3. Results

Study characteristics

A total of 7,311 suitable studies were identified using three online databases: Google Scholar, PubMed, and the Wiley online library. After removing duplicate research and inappropriate titles, 28 papers were evaluated for eligibility. Nineteen research were excluded because they did not match the inclusion and exclusion criteria; hence, fourteen studies met the eligibility criteria and were included in the qualitative analysis, as shown in Figure 1**.** The included studies comprise six cohorts (66.67%) and three case-control (33.33%) studies. These studies came from several countries such as Hungary, India, Iran, Korea, New Zealand, Portugal, and the USA.[6,8-12,14-16] All of the studies included premature infants at risk as study subjects consisted of 1,566 infants. The at-risk is all infants admitted to and treated in the neonatal

intensive care unit (NICU) with a gestational age of less than 34 weeks and a birthweight less than 2000 grams. All included studies then classified the at-risk infants as hyperglycemia and non-hyperglycemia. Hyperglycemia was defined as a plasma glucose concentration of more than 150 mg/dL (8.3 mmol/L) at least twice throughout the hospital stay.[8,12] The ROP status was assessed through initial ophthalmologic screening done by an ophthalmologist. Based on the sample characteristics, six studies found that the mean gestational age of infants in the ROP group was lower than the non-ROP group.[6,8,11-15] Based on the birth weight, six studies also found the birth weight of infants in the ROP group was smaller than the non-ROP group. While three other studies provided data regarding the mean of GA and BW globally for all study samples.[9,10,16] The detailed characteristics of the included studies are summarized in Table 1.

Quality assessment result of the study

Using the Newcastle Ottawa Scale (NOS), 8 of the 9 studies received scores in the range of 7-9, with the remaining studies receiving a score of 5, indicating satisfactory quality. The study's comprehensive quality assessment is shown in Table 2.

Mean glucose level and prevalence of hyperglycemia

Five of the nine studies reported differences in mean glucose levels between ROP and non-ROP groups. All five investigations found that the mean glucose level in the ROP group was greater than in the non-ROP group.[6,8,12,14,16] Study by Ahmadpour-Kacho et al. that included 155 infants with < 34 weeks GA and <2000 gram BW found the mean glucose level in the ROP and the non-ROP group were 147.53 ± 71.14 vs. 93.80 ± 37.37 mg/dL, respectively.[8] Garg et al. discovered that the mean glucose level in the ROP group was 12515 mg/dL, higher than the non-ROP group, which had a mean glucose level of 11118 mg/dL.[12] Kim et al. discovered comparable results in a study of 147 VLBW infants in Korea, with the mean glucose level for the ROP and non-ROP groups being 140.10 and 119.85 mg/dL, respectively.[14] Mohsen et al. and Vannadil et al. discovered significant differences in mean glucose levels between the ROP and non-ROP groups in their studies. They discovered 119.19 versus 97.10 mg/dL and 121.66 versus 96.47, respectively.[6,16] The maximum mean glucose level observed in the ROP group was 147.53 mg/dL, with a minimum of 119 mg/dL. In the non-ROP group, the maximum mean glucose level was 119.85 mg/dL, and the minimum was 93.80 mg/dL. For the prevalence of hyperglycemia, six of the nine studies showed the prevalence of hyperglycemia between the ROP and the non-ROP group. All six studies found that the prevalence of glycemia was much higher than in the non-ROP group.[6,8-11,16]

Hyperglycemia and retinopathy of prematurity (ROP) in VLBW infants

All included studies provided data regarding the relationship between hyperglycemia and ROP, together with the OR and RR. As seen in Table 1, eight studies found a significant relationship between hyperglycemia in VLBW infants. While only one study by Kim et al. found no significant relationship between them (p-value=0.225).[14] Study by Ahmadpour-Kacho et al. found a significant relationship between hyperglycemia and ROP with OR (95%CI) = 14.27 (5.16–39.50) and p-value <0.001.[8] While a study by Almeida et al., found that hyperglycemia is a significant risk factor of ROP in VLBW infants with a RR (95% CI) = 28.062 (7.881–99.924), p-value <0.001.[9] Case-control study by Ertl et al. and Garg et al. found significant relationship between hyperglycemia and ROP with an OR 3.15 (1.12–8.84) and 2.7 (1.003–7.27), respectively.[11,12] The other cohort studies by Chavez-Valdez et al., Mohamed et al., Mohsen et al., and Vannadil et al. found that hyperglycemia is a risk factor for ROP in VLBW infants with a RR 5.17 (1.40 19.16), 1.022 (0.99-1.06), 1.073 (1.004, 1.146), 1.77 (1.08-2.86), and 2.506 (1.287-4.882), respectively.[6,10,15,16]

Table 1. Characteristics of included studies.

Study	Study design	Study sample	GA weeks (Mean/Median)		BW gram (Mean/Median)		Blood glucose level (Mean±SD)		Hyperglycemia n (%)		p-value	OR or RR (95% CI)
			TOP	Non-ROP	ROP	Non-ROP	ROP	Non-ROP group	ROP group	Non-ROP group		
Ahmadpour-Kacho et al., 2014, Iran.[8]	Case-control	155 infants with < 34 weeks GA and <2000 gram BW.	29.91 ± 2.46	30.59 ± 1.97	1,238.57 ± 344.77	1,327.53 ± 293.03	147.53 ± 71.14	93.80 ± 37.37	33 (47.20)	5 (5.9)	<0.001	14.27 (5.16–39.50)
Almeida et al., 2021, Portugal.[9]	Cohort	152 infants with <32 weeks GA and <1500 gram BW.	32 (24-36)		1,240 (408-2,670)		NS	NS	24 (72.70)	6 (0.05)	<0.001	28.062 (7.881–99.924)
Chavez-Valdez et al., 2011, USA.[10]	Cohort	One hundred fourteen infants <1000 g were admitted to a level IV NICU.	26.6±2		782±136 g		NS	NS	64 (56.00)	50 (44.00)	0.014	5.17 (1.40 19.16)
Ertl et al., 2005, Hungary.[11]	Case-control	201 VLBW infants.	27.0±1.9	30.1±2.2	971±227	1,237±192	NS	NS	30 (76.92)	9 (23.08)	<0.05	3.15 (1.12–8.84)
Garg et al., 2003, USA.[12]	Case-control	Forty-seven infants with BW < 1000 grams.	24.7±0.8	25.1±0.86	685±91	734±121	125±15	111±18	NS	NS	0.041	2.7 (1.003–7.27)
Kim et al., 2017, Korea.[14]	Cohort	One hundred forty-seven VLBW infants.	27.3±1.5	30.5±2.7	952±199	1,240±219	140.10±36.30	119.85±27.68	NS	NS	0.225	1.022 (0.99-1.06)
Mohamed et al., 2013, USA.[15]	Cohort	582 infants with <32 weeks GA and <1500 g BW.	25.8 ± 1.9	28.1 ± 1.8	831 ± 266	1,080 ± 272	NS	NS	NS	NS	0.04	1.073 (1.004, 1.146)
Mohsen et al., 2014, USA.[6]	Cohort	Sixty-five infants with GA<32 weeks or BW < 1500 g.	30±1	31.5±0.9	1,227±204	1,450±202	119±19	97± 10	19 (61.29)	12 (38.71)	0.024	1.77 (1.08-2.86)
Vannadil et al., 2020, India.[16]	Cohort	One hundred-three risk infants of NICU in a tertiary care center in western India.	30.282±2.0188		1,251.621± 313.1432		121.66± 12.71431	96.475± 8.211515	23 (79.31)	6 (20.69)	<0.05	2.506 (1.287-4.882)

Abbreviation: BW=birth weight; GA=gestational age; NICU=neonatal intensive care unit; VLBW=very low birth weight.

Table 2. Quality study assessment using the Newcastle-Ottawa Scale (NOS).

Study	Selection	Outcome	Comparability	Total score
Ahmadpour-Kacho et al.[8]	4	2	3	9
Almeida et al.[9]	3	2	3	8
Chavez-Valdez et al.[10]	3	2	2	7
Ertl et al.[11]	4	2	3	9
Garg et al.[12]	3	2	2	7
Kim et al.[14]	2	1	2	5
Mohamed et al.[15]	3	2	3	8
Mohsen et al.[6]	4	2	3	9
Vannadil et al.[16]	4	2	2	8
Note: The selection item included the following criteria: representativeness of the exposed cohort, selection of the non-exposed group, exposure determination, and demonstration that the outcome of interest was not nonexistent at the start of the trial. The outcome parameters included cohort comparability based on the design or study that accounted for confounders. The comparability parameters were assessment of outcome, follow-up long enough for outcomes to occur, and adequacy of cohort follow-up.				

4. Discussion

This systematic review investigates the link between hyperglycemia and ROP in very low birth weight infants. A qualitative analysis of nine included studies found a strong connection between hyperglycemia and ROP in newborns with very low birth weight. Using cohort and case-control studies data, we discovered that the OR and RR of developing ROP were considerably greater in infants with hyperglycemia. The greatest OR reported was 28.062 (7.881-99.924), p-value 0.001. Very low birth weight infants with hyperglycemia also tend to increase the risk of ROP. This suggests that VLBW newborns with hyperglycemia are 28 times more likely than non-hyperglycemic neonates to have ROP.[9]

Retinopathy of prematurity is a multifactorial disease linked with microvascular degeneration defined by a halt in normal retinal angiogenesis. ROP develops and progresses as a result of numerous circumstances.[7] The two biggest risk factors for newborns having ROP are low birth weight and a young gestational time. Infants with very low birth weights, particularly those under 1000 g, experience hyperglycemia due to glucose intolerance. Many critically preterm newborns may have hyperglycemia during the first few weeks of life while receiving a continuous glucose infusion. It is found in 45% of all babies weighing less than 1,000 g and 80% of those weighing under 750 g. A neonate weighing less than 1000 g at birth is 18 times more likely to develop hyperglycemia than one weighing more than 2000 g.[8,11,17]

Even though the glucose infusion rate is sufficient to meet the basal requirement (4–7 mg/kg/min), transient neonatal hyperglycemia is frequently observed in extremely preterm neonates (30 weeks gestation) who receive parenteral feeding. Neonatal hyperglycemia is a significant problem that can result in osmotic diuresis, dehydration, weight loss, an increased risk of intraventricular hemorrhage, and a higher mortality rate. Compared to normoglycemic neonates, Mitanchez-Mokhtari et al. showed that hyperglycemic preterm infants had partial insulin resistance and faulty proinsulin processing in cells. These infants require greater insulin doses to reach euglycemia.[17-19]

One of the most difficult conditions to address in VLBW newborns is hyperglycemia. Once the umbilical cord is clamped, premature newborns must rely on a glucose infusion via peripheral or central catheters to maintain euglycemia. The condition is exacerbated further by impaired glucose tolerance, infection, and steroid therapy, all contributing to the variance in serum glucose levels that VLBW babies experience.[17-19]

It is still unclear exactly how hyperglycemia impacts ROP. Experimental investigations have demonstrated that neonatal mice exposed to early hyperglycemia exhibit ROP-like alterations, including neuronal loss and delayed retinal angiogenesis. The pathogenesis and progression of ROP are significantly influenced by neoangiogenesis and increased endothelial permeability, largely mediated by VEGF. In various animal models, VEGF expression is linked to the beginning of ischemia-induced intraocular neovascularization. The pathophysiologic link between excessive glucose levels and ROP may be represented by VEGF. In the Muller cells of the rat retina, Brooks et al. found that increasing the glucose level while under hypoxic conditions boosted the expression of the VEGF protein. VEGF was elevated at both the mRNA and protein levels in rat mesangial cells exposed to high hyperglycemia. A recent study linked low levels of insulin-like growth factor I present after delivery in preterm newborns with the development of ROP and the accumulation of VEGF in the retina.[7,17-19]

The American Ophthalmologist Association recommends ROP screening in infants with (i) birth weight below 1500 grams and gestational age below or equal to 32 weeks, (ii) birth weight 1500-2000 grams or above or equal to 32 weeks with a history of respiratory problems and requiring oxygen at birth, and (iii) all infant syndromes with risk factors such as respiratory problems, sepsis, congenital heart problems, history of blood transfusions, twin births and history of oxygen use for more than 28 days. ROP screening is performed by ophthalmologists trained and experienced in detecting ROP. ROP screening begins based on the gestational age. Screening is done 2-4 weeks after birth if the baby is at >30 weeks gestation. Four weeks after delivery, screening is done if the baby was born before 30 weeks of pregnancy. Before leaving the hospital for treatment, ROP screening is done at least once. ROP screening is done in perinatal medicine on infants receiving hospital care. ROP screening can be completed at the polyclinic for infants who have just left the hospital. During the screening, monitoring the infant's heart rate and oxygen saturation is necessary.[1,2,20]

Management of ROP is carried out based on the degree of disease. In mild cases of ROP, it is sufficient to observe the baby, and it can heal independently (spontaneous regression). However, in severe cases, babies must receive therapy through laser photocoagulation, cryotherapy, injecting anti-VEGF drugs into the eyeball, or surgery. This therapy aims to prevent the development of ROP, which can cause blindness. Apart from blindness, some complications that can occur in ROP include cataracts, glaucoma, strabismus (squint), and refractive errors (high myopia, astigmatism, or hypermetropia). Ours is the most recent systematic review examining the link between hyperglycemia and ROP in VLBW infants.[2,7,20]

This study has several limitations that should be considered. Firstly, the limited number of included studies may affect the generalizability of the findings. Additionally, the heterogeneity among the studies in terms of study design, population characteristics, and measurement of glucose levels introduces variability that can impact the overall conclusions. Alternative study designs, such as cohort studies with stricter control groups, could potentially mitigate this bias, although they may not reach the level of randomized controlled trials. Future research directions should investigate the effectiveness of specific interventions to manage hyperglycemia and reduce ROP risk. Such studies could provide clearer guidelines for neonatal care and improve outcomes for VLBW infants. This systematic review has been approved by the ethics committee of the Faculty of Medicine, Udayana University, with approval number No: 2356/UN14.2.2.VII.14/LT/2023.

5. Conclusion

Hyperglycemia is significantly associated with ROP and is a risk factor for the condition in VLBW infants. Managing hyperglycemia in these infants may reduce the risk of developing ROP. This review underscores the importance of vigilant monitoring and management of blood glucose levels in VLBW infants

to prevent ROP. Further research, including randomized controlled trials, is needed to establish effective interventions and confirm the findings of this review.

6. References

1. Ministry of Health of the Republic of Indonesia. Screening Retinopathy of Prematurity (ROP). 2023. Available from: https://yankes.kemkes.go.id/view_artikel/2032/skrining-retinopathy-of-prematurity-rop. (Accessed on: 12th July 2023).
2. Hong EH, Shin YU, Cho H. Retinopathy of prematurity: a review of epidemiology and current treatment strategies. Clin Exp Pediatr. 2022; 65(3): 115.
3. Au SC, Tang SM, Rong SS, Chen LJ, Yam JC. Association between hyperglycemia and retinopathy of prematurity: a systemic review and meta-analysis. Sci Rep. 2015; 5(1): 9091.
4. Ludwig CA, Chen TA, Hernandez-Boussard T, Moshfeghi AA, Moshfeghi DM. The epidemiology of retinopathy of prematurity in the United States. Ophthalmic Surg Lasers Imaging Retina. 2022; 48(7): 553–62.
5. Lei C, Duan J, Ge G, Zhang M. Association between neonatal hyperglycemia and retinopathy of prematurity: a meta-analysis. Eur J Pediatr. 2021: 1-10.
6. Mohsen L, Abou-Alam M, El-Dib M, Labib M, Elsada M, Aly H. A prospective study on hyperglycemia and retinopathy of prematurity. J Perinatol. 2014; 34(6): 453-57.
7. Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF, Retinopathy of prematurity: a review of risk factors and their clinical significance. Surv Ophthalmol. 2018; 63(5): 618-37.
8. Ahmadpour-Kacho M, Jashni Motlagh A, Rasoulinejad SA, Jahangir T, Bijani A, Zahed Pasha Y. Correlation between hyperglycemia and retinopathy of prematurity. Pediatr Int. 2014; 56(5): 726-30.
9. Almeida AC, Silva GA, Santini G, Brízido M, Correia M, Coelho C, et al. Correlation between hyperglycemia and glycated albumin with retinopathy of prematurity. Sci Rep. 2021; 11(1): 22321.
10. Chavez-Valdez R, McGowan J, Cannon E, Lehmann CU. Contribution of early glycemic status in the development of severe retinopathy of prematurity in a cohort of ELBW infants. J Perinatol. 2011; 31(12): 749-56.
11. Ertl T, Gyarmati J, Gaál V, Szabó I. Relationship between hyperglycemia and retinopathy of prematurity in very low birth weight infants. Neonatology. 2006; 89(1): 56-59.
12. Garg R, Agthe AG, Donohue PK, Lehmann CU. Hyperglycemia and retinopathy of prematurity in very low birth weight infants. J Perinatol. 2003; 23(3): 186-194.
13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010; 25: 603-5.
14. Kim SK, An JW, Lee SH, Oh YK. The relationship between hyperglycemia and retinopathy of prematurity in very low birth weight infants. Perinatology. 2017; 28(4): 127-33.
15. Mohamed S, Murray JC, Dagle JM, Colaizy T. Hyperglycemia as a risk factor for the development of retinopathy of prematurity. BMC Pediatr. 2013; 13(1): 1-5.
16. Vannadil H, Moulick PS, Khan MA, Shankar S, Kaushik J, Sati, A. Hyperglycaemia as a risk factor for the development of retinopathy of prematurity: a cohort study. Med J Armed Forces India. 2020; 76(1): 95-102.
17. Lee JH, Hornik CP, Testoni D, Laughon MM, Cotten CM, Maldonado RS, et al. Insulin, hyperglycemia, and severe retinopathy of prematurity in extremely low-birth-weight infants. Am J Perinatol. 2015; 393-400.
18. Hård AL, Smith LE, Hellström A. Nutrition, insulin-like growth factor-1 and retinopathy of

prematurity. In Seminars in Fetal and Neonatal Medicine. WB Saunders. 2013; 18(3): 136-142).

19. Mitanchez-Mokhtari D, Lahlou N, Kieffer F, Magny JF, Roger M, Voyer M. Both relative insulin resistance and defective islet β-cell processing of proinsulin are responsible for transient hyperglycemia in extremely preterm infants. Pediatrics. 2004; 113(3): 537-41.
20. Sitorus RS, Djatikusumo A, Andayani G, Barliana JD, Yulia DE. National Guidelines for Screening and Therapy of Retinopathy of Prematurity (ROP) in Premature Infants in Indonesia. 2011.