https://stikes-nhm.e-journal.id/NU/index

P-ISSN : 2085-5931
e- ISSN : 2085-5931
Sekolah Tinggi Ilmu Kesehatan Ngudia Husada Madura
Bekerja sama dengan Persatuan Perawat Nasional Indonesia (PPNI) Kabupaten Bangkalan
NURSING UPDATE
Jurnal Ilmiah Ilmu Keperawatan

Article

Risk Factors Neonatal Jaundice – Literature Review

Gitta Arinda Faustina[1], Esti Yunitasari[2], Dwiyanti Puspitasari[3]

[1]Program Studi Kebidanan, Fakultas Kedokteran Universitas Airlangga
[2]Departemen Keperawatan Maternitas dan Anak, Fakultas Keperawatan Universitas Airlangga
[3]Departemen Pediatri, Fakultas Kedokteran Universitas Airlangga

SUBMISSION TRACK

Recieved: August 04, 2021
Final Revision: August 23, 2021
Available Online: September 19, 2021

KEYWORDS

Neonatal Jaundice; Risk Factors; G6PD deficiency.

CORRESPONDENCE

Phone: +62 853 3088 3081

E-mail: gitta.arinda@gmail.com

A B S T R A C T

Jaundice adds 9% causes of infant mortality in Indonesia. Jaundice refers to the yellow coloration of the skin and sclera of the newborns that results from the accumulation of bilirubin in the skin and mucous membranes. This is associated with increased circulating bilirubin levels, a condition known as neonatal jaundice. Related risk factors in mothers and infants should be considered because jaundice may lead to complications, named kernicterus. This secondary study used literature review studies with published articles between 2015 and 2020. Search term of this articles used Boolean operator with the keywords "neonate OR newborn" AND "jaundice OR hyperbilirubinemia" AND "risk factors". There were 801 articles of literature from 3 databases, PubMed, Scopus, and Science Direct. The final results obtained 14 articles in accordance with the inclusion and exclusion criteria. The following results were obtained 6 articles said that G6PD deficiency was a risk factor for neonatal jaundice, 3 articles said ABO incompatibility, and also there are several articles said obesity in pregnancy, gestational ages, and breastfeeding were risk factor for neonatal jaundice. Identification of factors affecting the incidence of jaundice can be effective in preventing susceptible predisposing factors in newborns and high-risk mothers.

I. INTRODUCTION

Based on the results of Survei Demografi dan Kesehatan Indonesia (SDKI) in 2017, it shows that 63% of infant deaths occur within 1 month after birth, where neonatal jaundice accounts for 6% of neonatal deaths per 1,000 live births in Indonesia (Kementrian Kesehatan RI 2018). Neonatal jaundice is the most common morbidity found in the neonatal period. As many as 65% of newborns experience jaundice in the first week of birth and 80% of infants with premature birth (Devi dan Vijaykumar 2016). In Indonesia, in 2018, there were 46.8% of 844 neonates who experienced neonatal jaundice in the NICU of RSUD Soetomo Surabaya (Auliasari et al. 2019).

Jaundice in newborn refers to the yellow discoloration of the skin and sclera of the newborn's eyes resulting from the accumulation of bilirubin in the skin and mucous membranes. It is associated with increased levels of circulating bilirubin, a condition known as neonatal jaundice (Welsh 2010).

Severe jaundice can suppress oxygen consumption and suppress oxidative phosphorylation causing brain cell damage, resulting in neuronal dysfunction and encephalopathy (Sulistijono et al. 2010). Babies with severe neonatal jaundice are at risk for death or disability in their life. Associated risk factors in infants must be considered because jaundice may lead to complications, named kernicterus (Thielemans et al. 2018).

II. METHODS

This research is a secondary study using a literature review studies from 3 databases, PubMed, Scopus, and Science Direct. Search term using Boolean operator with the keywords "neonate OR newborn" AND "jaundice OR hyperbilirubinemia" AND "risk factors". The inclusion criteria of this study are: (1) literature in English; (2) published articles between 2015 and 2020; (3) open access; (4) full-text accessible literature. Exclusion criteria are: (1) Non-primary studies such as review article, case report, conference result or book chapters; (2) non-pregnant women; (3) new born with congenital abnormalities. The final results obtained 14 articles in accordance with the inclusion and exclusion criteria.

III. RESULT

There were 801 literature articles from 3 databases, including Scopus with 242 articles, Pubmed with 294 articles and Sience Direct with 265 articles. All articles that have been found are then collected for screening used PRISMA Flowchart. The results of the PRISMA flowchart in the literature search are shown in Figure 1.

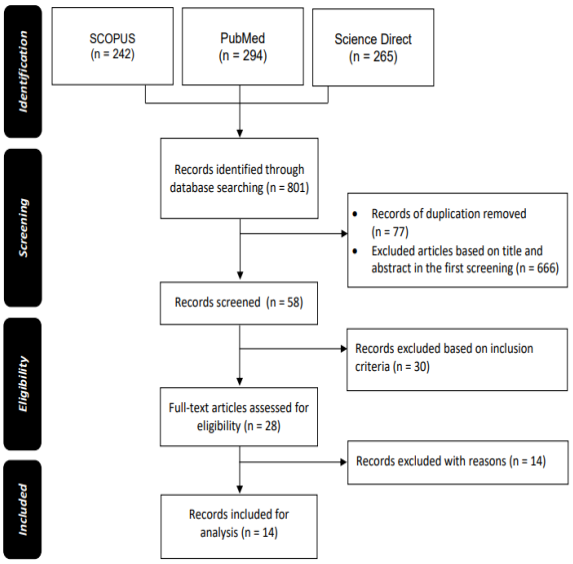

Figure 1. PRISMA Flowchart of screening process**.**

Literature Quality Assessment

The literature quality assessment was carried out using the quality assessment tool for quantitative studies from the Effective Public Health Practice Project (EPHPP). In the EPHPP there are 8 question points and the results of each question are in the form of a value of 1 which means the quality of the literature is strong, a value of 2 which means moderate, and a value of 3 which means weak.

Table 1. Summary of literature included for analysis

Author(s) / year	Title	Methods	Finding (the most valued characteristic)	EPHPP
(Mojtahedi et al. 2018)	*Risk Factors Associated with Neonatal Jaundice: A Cross- Sectional Study from Iran*	Cross-sectional	Gestational age was associated with jaundice (P < 0.05). The results showed that the risk of neonatal jaundice increased significantly with decreasing gestational age. In addition, there was a significant association between various bilirubin levels and G6PD (P < 0.05).	1
(Rougée, Miyagi, dan Collier 2016)	*Obstetric Obesity is Associated with Neonatal Hyperbilirubinemia with High Prevalence in Native Hawaiians and Pacific Island Women*	Retrospect-ive study	Results show that obesity during pregnancy is associated with increased maternal and infant unconjugated bilirubin	2
(Zhou et al. 2018)	*Identification of Genetic Risk Factors for Neonatal Hyperbilirubinemia in Fujian Province, Southeastern China: A Case-Control Study*	Case control study	Based on the results of multivariate logistic regression analysis, blood-group incompatibility was found, G6PD deficiency was detected in the group of cases of neonatal jaundice.	2
(Devi dan Vijaykumar 2016)	*Risk Factors For Neonatal Hyperbilirubinemia: A Case Control Study*	case control study.	Based on the results of the study, there was a relationship between neonatal jaundice and premature birth, low birth weight, breast milk	2
(Isa et al. 2017)	*Neonatal indirect hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency*	Case control study	Among 1,046 jaundiced patients, 442 (42%) had G6PD deficiency.	2
(Norman et al. 2015)	*Predicting Nonhemolytic Neonatal Hyperbilirubinemia*	Case control study	Risk factors associated with neonatal jaundice include gestational age 37-38 weeks, vacuum extraction, primiparas, maternal obesity.	1
(Weng et al. 2018)	*Risk assessment of gene variants for neonatal hyperbilirubinemia in Taiwan*	Cohort study	The incidence of prolonged jaundice is 32.2%. Prolonged jaundice was more common in infants with exclusive breastfeeding (p<0.001)	1
(Brits et al. 2018)	*The prevalence of neonatal jaundice and risk factors in healthy term neonates*	Cross-sectional study	The prevalence of neonatal jaundice was 55.2%. Normal delivery is the only risk factor associated with neonatal jaundice	3
(Tavakolizadeh R, Izadi A, Seirafi G, Khedmat L 2018)	*Maternal risk Factors for Neonatal Jaundice: a Hospital-Based Cross-Sectional Study in Tehran.*	Cross – sectional study	The results showed that BMI and primipara were associated with an increase in bilirubin.	1
(Campbell dan Mena 2019)	*Severe hyperbilirubinemia in newborns, risk factors and neurological outcomes*	Retrospectiv e study	The main risk factors for elevated bilirubin are prematurity, excessive weight loss	2

(Kasemy et al. 2020)	*prevalence of and mothers' knowledge, attitude and practice towards glucose-6-phosphate dehydrogenase deficiency among neonates with jaundice: A cross-sectional study*	Cross-sectional study	Neonates with G6PD deficiency showed higher bilirubin levels (p < 0.001)	2
(Bozkurt et al. 2020)	*Severe neonatal hyperbilirubinemia in the southeast region of turkey*	Cohort Study	The most common etiology for severe hyperbilirubinemia was hemolytic (44.3%) with ABO blood incompatibility being the main cause (30.4%). There are 15 babies caused by G6PD deficiency (13%)	1
(Weng et al. 2018)	*Risk assessment of prolonged jaundice in infants at one month of age: A prospective cohort study*	cohort	The results showed that the most influential risk factor for prolonged jaundice was 35-37 weeks of gestation, exclusive breastfeeding.	1
(Thielemans et al. 2017)	*Neonatal Hyperbilirubinemia in a Marginalized Population on the Thai-Myanmar Border: A study protocol*	Cohort	The most frequently reported risk factors associated with neonatal jaundice are G6PD deficiency, and potential ABO incompatibility.	2

IV. DISCUSSION

Risk Factor of Neonatal Jaundices

1. G6PD Deficiency

Based on the 14 articles that have been analyzed, there are 6 articles that show that G6PD deficiency is a risk factor for neonatal jaundice. In the study of Najib, et al (2013) showed that there were 25.5% of the causes of jaundice caused by G6PD deficiency. (Bozkurt et al. 2020) conducted a study in Turkey with 115 newborns diagnosed with neonatal jaundice and found that 13% or as many as 15 babies jaundice was caused by G6PD deficiency.

G6PD deficiency has a very large effect on red blood cells because the G6PD enzyme is needed to produce energy to maintain red blood cells, carry oxygen, regulate ion and water transport into and out of cells, and help remove carbon dioxide and protons formed in tissue metabolism. When levels of the G6PD enzyme decrease, red blood cells experience a lack of energy and changes in shape which facilitate lysis when there is oxidant stress (Wibowo 2007). The lysis of red blood cells can cause an increase in the production of unconjugated bilirubin which is one of the causes of neonatal jaundice (Maryanti 2011).

2. ABO Incompatibilities

There are 3 articles discuss the relationship between ABO incompatibility and neonatal jaundice. (Bozkurt et al. 2020) who conducted a study in Turkey said that 30.4% of infants with ABO blood type incompatibility were the main cause of the formation of jaundice. In the study of Shetty, et al (2015) the incidence of ABO incompatibility was 42.5% in infants with jaundice. Research conducted by Auliasari (2019) at RSUD Dr. Soetomo Surabaya also revealed that ABO incompatibility increased the incidence of neonatal jaundice by 6.833 times compared to neonates who did not

experience ABO incompatibility (Auliasari et al. 2019).

ABO incompatibility occurs when a mother with blood type O becomes pregnant with a fetus with a different blood type (type A, B, or AB). Some mothers have relatively high levels of anti-A or anti-B Immunoglobulin G (IgG) that cross the placenta so that they have the potential to cause erythroblastosis (Özcan et al. 2017). Maternal serum contains anti-A and anti-B naturally, which can cause hemolysis and the result in increased production of bilirubin (Maryanti 2011)

3. Obese Mother

Norman, et al (2017) conducted a study with 23,711 neonates who were diagnosed with neonatal jaundice. The results showed that 9.04% of obese mothers gave birth to babies with jaundice. Rougee (2016) also reported that obesity in pregnant women was significantly associated with increased bilirubin in neonates.

Obesity is related to the regulation of the protein UGT1A1 causing changes in bilirubin levels. When a person is obese, the liver will enlarge and there will be an increase in liver volume so that compensation occurs by lowering the UGT1A1 protein level (per hepatocyte) to a threshold (Rougée et al. 2016). The role of enzyme UGT1A1 in bilirubin metabolism is processing of hepatic glucuronidation of bilirubin (Yang et al. 2016). If there is a deficiency in the UGT1A1 enzyme, the bilirubin concentration will increase. UGT1A1 is a specific isoform that plays in conjugation of bilirubin and is part of the UDPGT enzyme. If there is no glucuronyl transferase enzyme in the body, the unconjugated bilirubin concentration will increase (Kemenkes RI 2012)

4. Gestational Ages

65% of newborns experience jaundice in the first week of birth and 80% of infants with premature birth. In India, it was shown that there were 21% cases of infant jaundice at low gestational age (Devi dan Vijaykumar 2016). The results of the study reported by Weng, Yi Hao., et al (2018) said that the gestational age of 35-37 weeks increased the incidence of neonatal jaundice by 2,468 times.

Preterm infants are more likely to experience neonatal jaundice. Neonatal jaundice in premature infants is caused by excessive destruction of red blood cells because of immature liver (Panna Choudhury et al. 2013). Therefore, it takes more of time for conjugation of indirect bilirubin to direct bilirubin (Behrman, Richard E., Kliegman, Robert M., Arvin 2000). In addition, the risk of dehydration in preterm infants can occur due to low *oromotor* abilities and nerve function that can lead to weight loss in infants and decreased bilirubin excretion which causes jaundice (Bhutani 2012)

5. Breastfeeding

Weng, Yi Hao., Cheng, Shao Wen., Yang, Chun Yuh et al (2018) said that the risk of neonatal jaundice increased by 6,234 times in infants with exclusive breastfeeding than infants who did not use exclusive breastfeeding. In a multivariate analysis conducted by Hwang, Nu Ri and Jin Kyu Kim (2016), they reported that exclusive breastfeeding had a 3.91 times higher risk of developing neonatal jaundice than infants who did not use exclusive breastfeeding. Devi, D.S and Vijaykumar (2017) said that a decrease in the frequency of breastfeeding showed an increase in jaundice.

In breastfeeding infants there are two forms of neonatal jaundice, early and late onset. The form of early onset is associated with the frequency and less

intake of breastfeeding that causes dehydration or lack of caloric intake. This process is enhanced in the newborn's gut due to a lack of normal enteric bacteria that break down bilirubin into urobilinogen; These bacteria also increase the activity of the enzyme -glucuronidase which hydrolyzes the conjugated bilirubin back to unconjugated state (if this bilirubin returns to the state in the system) (Karen J. Marcdante et al. 2013).

While late onset is influenced by the ingredients of breast milk which affects the process of conjugation and excretion. The cause of late onset is unknown, but it has been linked to the presence of breast milk-specific factors, 2α-20β-pregnidiol, which affects the activity of the enzyme uridine disphosphate glucuronocyl transferase or UDPGT which affects the release of conjugated bilirubin from hepatocytes or other factors that may cause an increase in the enterohepatic pathway.

V. CONCLUSION

There are several risk factors of neonatal jaundice are obtained from prenatal factors such as ABO incompetence and obesity. In intranatal factors can be caused by gestational age. In addition, postnatal factors also increase the incidence of neonatal jaundice are G6PD deficiency and low intake of exclusive breastfeeding. Based on the results of the articles analyzed by the authors, the most common factor for neonatal jaundice is G6PD deficiency.

Therefore, regular care seems to be needed during pregnancy, including the provision of good nutrition for pregnant women. Moreover, follow-up of the baby is required in case of complications in pregnancy such as ABO incompatibility, obesity that occurs during pregnancy, which are also important causes of neonatal jaundice. In addition, providing information and training on good breastfeeding techniques and general screening of infants with blood tests or skin bilirubin levels before discharge from the hospital is an effective way to reduce the risk of neonatal jaundice (M. Sholeh Kosim et al. 2014).

REFERENCES

Auliasari, Nimas Anggie, Risa Etika, Ilya Krisnana, dan Pudji Lestari. 2019. "Faktor Risiko Kejadian Ikterus Neonatorum." *Pediomaternal Nursing Journal* 5(2):1–90. doi: 10.20473/pmnj.v5i2.13457.

Behrman, Richard E., Kliegman, Robert M., Arvin, Ann M. 2000. *Ilmu Kesehatan Anak edisi 15 vol. 3*. 15 ed.

Bhutani, Vinod K. 2012. "Late Preterm Births: Major Cause of Prematurity and Adverse Outcomes of Neonatal Hyperbilirubinemia." 704–5.

Bozkurt, Özlem, Ebru Yücesoy, Baran Oğuz, Ömür Akinel, Mehmet Fatih Palali, dan Nurgül Ataş. 2020. "Severe neonatal hyperbilirubinemia in the southeast region of turkey." *Turkish Journal of Medical Sciences* 50(1):103–9. doi: 10.3906/sag-1906-22.

Brits, Hanneke, Jeanie Adendorff, Dyanti Huisamen, Dahne Beukes, Kristian Botha, Hanre Herbst, dan Gina Joubert. 2018. "The prevalence of neonatal jaundice and risk factors in healthy term neonates at National District Hospital in Bloemfontein." *African Journal of Primary Health Care & Family Medicine* 10(1):1–6. doi: 10.4102/phcfm.v10i1.1582.

Campbell, Stephanie, dan Patricia Mena. 2019. "Severe hyperbilirubinemia in newborns , risk factors and neurological outcomes Hiperbilirrubinemia severa en Recién Nacidos , factores de riesgo y secuelas." 90(3):267–74. doi: 10.32641/rchped.v90i3.772.

Devi, D. Sumangala, dan Bindu Vijaykumar. 2016. "Risk factors for neonatal hyperbilirubinemia: a case control study." *International Journal of Reproduction, Contraception, Obstetrics and Gynecology* 6(1):198–202. doi: 10.18203/2320-1770.ijrcog20164657.

Isa, Hasan M., Masooma S. Mohamed, Afaf M. Mohamed, Adel Abdulla, dan Fuad Abdulla. 2017. "Neonatal indirect hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency." *Korean Journal of Pediatrics* 60(4):106–11. doi: 10.3345/kjp.2017.60.4.106.

Karen J. Marcdante, Robert Kliegman, Hal Jenson, dan Richard Behrman. 2013. *Nelson Ilmu Kesehatan Anak Esensial 6th Edition*. diedit oleh IDAI.

Kasemy, Zeinab A., Wael A. Bahbah, Sally M. El Hefnawy, dan Safa H. Alkalash. 2020. "Prevalence of and mothers' knowledge, attitude and practice towards glucose-6-phosphate dehydrogenase deficiency among neonates with jaundice: A cross-sectional study." *BMJ Open* 10(2). doi: 10.1136/bmjopen-2019-034079.

Kemenkes RI. 2012. *Buku Saku Pelayanan Kesehatan Neonatal Esensial*. Jakarta: Direktorat Jendral Bina Gizi dan Kesehatan Ibu dan Anak.

Kementrian Kesehatan RI. 2018. *Survei Demografi dan Kesehatan Indonesia*.

M. Sholeh Kosim, Ari Yunanto, Rizalya Dewi, dan Gatot Irawan Sarosa. 2014. *Buku ajar neonatologi*. Palembang: IDAI.

Maryanti, Dwi. 2011. *Buku Ajar Neonatus, Bayi dan Balita*. Jakarta: Trans Info Media.

Mojtahedi, Sayed Yousef, Anahita Izadi, Golnar Seirafi, Leila Khedmat, dan Reza Tavakolizadeh. 2018. "Risk Factors Associated with Neonatal Jaundice : A Cross-Sectional Study from Iran." 6(8):1387–93.

Norman, Mikael, Katarina Åberg, Karin Holmsten, Vania Weibel, dan Cecilia Ekéus. 2015. "Predicting nonhemolytic neonatal hyperbilirubinemia." *Pediatrics* 136(6):1087–94. doi: 10.1542/peds.2015-2001.

Özcan, Murat, Selin Sevinç, Vildan Boz Erkan, Yüksel Yurdugül, dan S. Ümit Sarıcı. 2017. "Hyperbilirubinemia due to minor blood group (anti-E) incompatibility in a newborn :

a case report." 162–64. doi: 10.5152/TurkPediatriArs.2017.2658.
Panna Choudhury, Arvind Bagga, Krishan Chugh, HPS Sachdev, Siddarth Ramji, dan Ramesh K. Puri. 2013. *Principles of Pediatric & Neonatal Emergencies*. 2/e. New Delhi, India.
Rougée, Luc Ra, Shogo J. Miyagi, dan Abby C. Collier. 2016. "Obstetric Obesity is Associated with Neonatal Hyperbilirubinemia with High Prevalence in Native Hawaiians and Pacific Island Women." *Hawai'i journal of medicine & public health : a journal of Asia Pacific Medicine & Public Health* 75(12):373–78.
Sulistijono, Eko, Ingga Gebyarani, M. Fahrul Udin, Brigitta Corebima, dan Siti Lintang K. 2010. "Pengaruh Karakteristik Demografis , Klinis dan Laboratorium pada Neonatus dengan Hiperbilirubinemia The Role of Demographic , Clinical and Laboratory Characteristics in Infant with Hyperbilirubinemia." 26(4):191–94.
Tavakolizadeh R, Izadi A, Seirafi G, Khedmat L, Mojtahedi SY. 2018. "Maternal risk Factors for Neonatal Jaundice: a Hospital-Based Cross- Sectional Study in Tehran." *Eur J Transl Myol 2018* 28(3):257–64.
Thielemans, L., M. Trip-Hoving, J. Landier, C. Turner, T. J. Prins, E. M. N. Wouda, B. Hanboonkunupakarn, C. Po, C. Beau, M. Mu, T. Hannay, F. Nosten, B. Van Overmeire, R. McGready, dan V. I. Carrara. 2018. "Indirect neonatal hyperbilirubinemia in hospitalized neonates on the Thai-Myanmar border: A review of neonatal medical records from 2009 to 2014." *BMC Pediatrics* 18(1):1–11. doi: 10.1186/s12887-018-1165-0.
Thielemans, Laurence, Margreet Trip-Hoving, Germana Bancone, Claudia Turner, Julie A. Simpson, Borimas Hanboonkunupakarn, Michaël Boele van Hensbroek, Patrick van Rheenen, Moo Kho Paw, François Nosten, Rose McGready, dan Verena I. Carrara. 2017. "Neonatal Hyperbilirubinemia in a Marginalized Population on the Thai-Myanmar Border: a study protocol." *BMC Pediatrics* 17(1):32. doi: 10.1186/s12887-017-0798-8.
Welsh, Andrew. 2010. *Neonatal jaundice.*
Weng, Yi Hao, Shao Wen Cheng, Chun Yuh Yang, dan Ya Wen Chiu. 2018. "Risk assessment of prolonged jaundice in infants at one month of age: A prospective cohort study." *Scientific Reports* 8(1):6–11. doi: 10.1038/s41598-018-33249-6.
Wibowo, Satrio. 2007. "PERBANDINGAN KADAR BILIRUBIN NEONATUS DENGAN DAN TANPA DEFISIENSI GLUCOSE-6-PHOSPHATE DEHYDROGENASE, INFEKSI DAN TIDAK INFEKSI."
Zhou, Jinfu, Changyi Yang, Wenbin Zhu, Shuwei Chen, Yinglin Zeng, Jing Wang, Hong Zhao, Yao Chen, dan Feng Lin. 2018. "Identification of Genetic Risk Factors for Neonatal Hyperbilirubinemia in Fujian Province, Southeastern China: A Case-Control Study." *BioMed Research International* 2018:1–8. doi: 10.1155/2018/7803175.

BIOGRAPHY

Gitta Arinda Faustina was born in Jember, Indonesia on September 19th 1998; received Bachelor of Midwife degree from Airlangga University in 2020 and currently study in Practicing Midwife Program in Airlangga University. Email: gitta.arinda@gmail.com

Esti Yunitasari, graduated for Bachelor degree from Univeritas Indonesia in 2000; graduated for master degree in 2008; and obtained PhD in 2016. Esti Yunitasari is currently lecturer in Airlangga University Nursing Program.

Dwiyanti Puspitasari received medical degree from Airlangga University in 1999; received master degree from Mahidol University in 2011; and specialized in Pediatric in 2012. Dwiyanti Puspitasari is currently lecturer in Airlangga Univeristy Faculty of Medicine.