Jurnal Healthsains
Printed ISSN: 2722-7782
Electronic ISSN:2722-5356
jurnal.healthsains.co.id

RELATIONSHIP BETWEEN DELIVERY METHOD WITH NEONATAL HYPERBILIRUBINEMIA

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Keywords:
Neonatal Hyperbilirubinemia, caesarean section

ABSTRACT

Jaundice in newborn was the most leading cause for hospitalization in newborns. It was manifest as yellowish discoloration of mucosa membrane caused by increase in serum or plasma bilirubin. This condition can be cause either by increased production breakdown of red blood cells, disorder in conjugation or impaired excretion. Meanwhile, some research also stated that delivery method can influence bilirubin concentration in newborn. This study was conducted to determine relationship between delivery method with neonatal hyperbilirubinemia that already receive phototherapy. As much as 104 babies with hyperbilirubinemia were included into this observational research. Around 55% of them, neonates were delivered by caesarean section. In conclusion, caesarean section method of delivery is associated with neonatal hyperbilirubinemia (p value 0.001).

INTRODUCTION

Jaundice or yellowish discoloration in newborn was the common cause of anxiety in parents leading to hospital. Hyperbilirubinemia is a term often used to describe an increase in total serum bilirubin in newborn less than one month old with concentration greater than 5 mg/dL. This condition could happen by physiological or pathological etiology. Hyperbilirubinemia is found approximately 60% of term babies and 80% of premature babies that were hospitalized, especially at first week of life. Physiological hyperbilirubinemia occurs in healthy and active infants, above 24 hours of age and will decrease slowly before two weeks of life. Meanwhile in pathological hyperbilirubinemia occurs before 24 hours of age with elevated total bilirubin levels serum more than 2 mg/dL/day followed by signs of vomitus, lethargy, inability to breastfeed, rapid weight loss, tachypnea and unstable body temperature. Some of severe hyperbilirubinemia could lead to devastating complication such as kern-icterus, refers to deposition of bilirubin in inner nuclei of the brain, basal ganglia that could manifest as chronic form of bilirubin encephalopathy. This condition will induce cerebral like symptoms such as

athetoid palsy, hearing loss, failure of upward gaze, lethargy, hypotonia followed by hypertonia (retro-collis and opisthotonus), irritable, apnea and seizure.

Nowadays, many newborns were delivered by caesarean section because of social indication. Despite of this elective procedure, some absolute indications of caesarean section delivery are fetal distress, macrosomia, cephalopelvic disproportion, breech position and placental problems such as placenta previa, eclampsia or in some cases multiple pregnancy as relative indication. Before caesarean section procedure, all of the mothers would be given antibiotic prophylaxis to prevent infection that can cause microbiota dysbiosis. This phenomenon was believed to be the potential mechanism of hyperbilirubinemia neonatorum. There has been some research on the relationship between jaundice in neonates and method of delivery. Therefore, this study aim to determine relationship between method of delivery with hyperbilirubinemia neonates at RSUP Kandou Manado.

RESEARCH METHODS

The research method was an observational analytic study with cross-sectional method. This observational study was conducted in Neonatology Intensive Care unit Prof. Dr. R. D. Kandou Manado Hospital within ten months from November 2022 until August 2023 with total sample of 104 neonates. The inclusion criteria include newborn age 0 – 7 days that had neonatal hyperbilirubinemia with 36-38 weeks of gestational age. On the other hand, the exclusion criteria include neonatal diagnosed with sepsis, hepatocellular disease, TORCH infection, HIV infection, Hepatitis B infection, multiple congenital anomalies, direct hyperbilirubinemia and was done phototherapy before experiment. This study was approved by Kandou Hospital Research and Ethics Committee and informed consent was obtained from parents. Sampling was done by purposive sampling that met inclusion criteria.

The collected data will be processed using SPSS version 22. Univariate analysis was present within distributive table and parametric data were present in median and standard deviation. Bivariate analysis was using *chi-square* test. The confidence interval was set to 95% and the margin of error accepted was 5%, p-value considered significant if p-value < 0.05 and highly significant if p-value < 0.01.

RESULTS AND DISCUSSION

Indirect hyperbilirubinemia usually appears on first week of life and present around 60 – 80% of all neonates. In general, this condition will improve within first weeks of life. In the other hand, caesarean section was usually preferred by women to delivered their babies because of its practical reason to be more elective surgery and can choose for its date. Among many benefits of caesarean section there are some side effects for its procedure such as dysbiosis microbiota. Microbiota is a collection of microorganisms that form ecological community in a particular area. While the microbiome refers to the collective genome of all the microorganisms that inhabit a region environment. Terminology "microbiota" (microbial taxa associated with humans) and the “microbiome” (a catalog of these microbes and their genes) are often used alternately. The number of gastrointestinal microbiota species varies, consists of more than 1000 species and more than 7000 strains, with the majority are the

species Bacteriodetes and Firmicutes. It is believed that antibiotic prophylaxis before caesarean section procedure will cause dysbiosis and disturb microbiota in the gut.

Characteristics of Research Samples

This study was conducted on neonates with hyperbilirubinemia which were treated at the Neonatology Intensive Care Unit of RSUP Prof. Dr. R. D. Kandou Manado with total sample of 104 neonates. Those 104 neonates who were selected by consecutive sampling were observed and analyze with cross-sectional study. Of the 104 respondents, 55 (53%) were female patients. The average median birth weight of patients ranged from 3015 grams while the patient's birth length had an average median of 48 cm. A total of 104 infants had high total bilirubin levels with an average total bilirubin level of 11.42 mg / dL with direct bilirubin having an average of 9.22 mg/ dL. The proportion of cases of indirect hyperbilirubinemia in cesarean section births is higher than normal births, which is 54.8%.

Table 1. Characteristic samples

Variable	**Total n=104**
Sex (%)	
Male	49 (47.1)
Female	55 (52.9)
Birth weight, mean (SD)	3015.67 (342.55)
Birth length, median (IQR)	48 (47-48.7)
Delivery method (%)	
Spontan per vaginam	47 (45.2)
Caesarean section	57 (54.8)
Total bilirubin concentration, mean (SD)	11.42 (8.85)
Indirect bilirubin concentration, mean (SD)	9.22 (6.97)

Bivariate Analysis of Research Variables

The results showed below stated that there was no significant relationship sex of infants with indirect hyperbilirubinemia between male or female babies. In this study, there were no significant relationship between birth weight in indirect hyperbilirubinemia neonatorum. Several studies suggest significant association between birth weight and the incidence of jaundice in infants. This may be because low birth weight tends to be associated with premature birth, resulting in immature liver function and shorter erythrocyte life span to only 90 days. But in this study, researcher only collect babies that born aterm within 38 – 39 weeks of gestational age so it will interfere with the birth weight result that include in the analysis. Based on birth length, there was no significant relationship between birth length and indirect hyperbilirubinemia in newborns. To be surprised, method of delivery imposed a great significancy for indirect hyperbilirubinemia in newborns with p-value 0.001.

Table 2. Bivariate Analysis

Variable	Total N=104	95% CI	Odds Ratio	P value
Sex (%)		0.19 – 0.55	0.179	0.326
Male	49 (47.1)			
Female	55 (52.9)			
Birth weight, mean (SD)	3015.67 (342.55)	0.00 – 0.12	0.000	0.113
Birth length, median (IQR)	48 (47-48.75)	0.05 – 0.23	0.090	0.497
Method of delivery (%)		1.31 – 2.47	1.835	0.001
Vaginal delivery	47 (45.2)			
Caesarean section	57 (54.8)			

As describe before, method of delivery has a significant relationship with neonatal hyperbilirubinemia. Babies born by caesarean section will develop neonatal jaundice 1.835 times rather than babies born by vaginal delivery (1.31 – 2.47 95% CI).

Studies have found that mode of delivery also influences the severity of jaundice, one of them is caesarian section that usually not indicated for the mothers are considered as risk factor. Study by Temok et al stated that newborns jaundice was more prevalent in neonates born by caesarean section rather than spontaneous delivered. On the other hand, studies by Chang et al was determine that newborns delivered naturally were more likely to develop jaundice rather than caesarean section. This study was supported by the likelihood of babies to develop birth trauma such as cephalhematoma, vacuum assisted vaginal delivery would increase production pathway that will interfere bilirubin metabolism and thus cause jaundice in newborns.

Other research done by Chang et al also stated that use of oxytocin in normal vaginal delivery will influence bilirubin metabolism that cause jaundice. Oxytocin with its hypo-osmotic effect will bring water retention into red blood cells of the newborns. Those things will advance the likelihood of red blood cells lysis in newborns and disturb the production imbalance in bilirubin metabolism.

Previous research conducted by Arisandi et al. showed that babies born by caesarean section with oxytocin induction had a higher risk of indirect hyperbilirubinemia compared to babies born spontaneously. This can be because in babies with normal births, breastfeeding is done in 6 hours or faster than in caesarean sections. As soon as the mother gave breastfeed to the newborn, it will reduce the likelihood of jaundice.

Not only that, another study conducted by Mariana et al stated that babies born by caesarean section also experience microbiota dysbiosis which affects bilirubin metabolism. The vaginal birth canal has colonization of good bacteria in the form of Lactobacillus, Prevotella, Bacteroides and Bifidobacterium microbiota while babies born by caesarean section will get prophylactic antibiotics given to their mothers, which will also affect the

microbiota in the baby and during labor where microbiota diversity is reduced. The process of delivery by sectio caesaria has the same bacterial colonization as bacterial colonization on the skin. The process of vaginal delivery is more recommended because it has microbiota transmission that is conducive to the formation of early microbiota initiation in the neonatal period in epithelial cell activation, immune system and allergy risk. However, other studies have shown that there is no significant difference in the risk of indirect hyperbilirubinemia between babies born by cesarean section and babies born spontaneously.

Generally, the antibiotics that has been used for prevention of infection before caesarean section are cephalosporin. Administration of antibiotics on all microbiota has a greater effect compared to other factors, and preliminary studies have been conducted to determine its impact. The gut microbiota in adults does not appear to be resistant to repeated courses of antibiotics. The same antibiotic affects certain microbes differently depending on the rest of the microbiome. possible due to the different growth phases, metabolic states, or contextual microbial networks in which the microorganisms reside. There is increasing evidence that antibiotics early in life have profound effects on the gut microbiota that may result in the development of several diseases later in life and other disorders.

Colonization of the microbiome occurs in early years of life. During and immediately after birth, newborns are exposed to maternal and environmental microbes that initiate the formation of the gut microbiome. In the first year of life, it is estimated that 10^{13} to 10^{14} microbes/ml consisting of 500-1000 species colonize the digestive tract. Many factors influence the formation of a baby's microbiota, such as pregnancy, mode of delivery, and mode of feeding. The mode of delivery plays an important role in the composition of the microbiota that persists in infants. In vaginal delivery, vaginal microbes such as Lactobacillus spp, Bifidobacterium, and Prevotella colonize the child, while newborns born via cesarean section are colonized by maternal skin microbiota, Corynebacterium, Staphylococcus, and Propionibacterium spp. In addition, the mode of feeding plays an important role in establishing a strong gut microbiota in infants. Breast milk contains more than 700 bacterial species and oligosaccharides that reinforce specific bacteria such as Bifidobacteria, immunoglobulins such as IgG and IgA, and cytokines such as TGF-β and interleukin 10 (IL-10), and the combined effect of these factors influences the selection of bacteria to colonize the urinary tract digestion of breastfed babies. Weaning and introduction of solid foods increases the diversity of the gut microbiota and increases butyrate-producing species, such as Clostridium, Prevotella, and Ruminococcus species. By the age of three, the composition of the gut microbiota becomes similar to that of adults.

In our observational study, the peak incidence of neonatal jaundice was approximately on third until fifth days. We suggest for all clinicians to observe carefully especially on these periods of time, despite of its mode of delivery whether vaginally nor caesarean section.

Limitations

In our study, we found some weaknesses for not generalized the type of feeding of these newborns. Some of them receive breastmilk while the other receive formula milk that will influence the microbiome and thus will affect the bilirubin metabolism itself. Not only that,

initial mother's medical history during pregnancy didn't recognize such as hypertension, eclampsia, diabetes and maternal blood or rhesus type that some of the disease will also influence the microbiome itself. Sample size was normal birth weight with newborns with term gestational age, so the generalization of the results was only in the group of babies with these conditions. Blood type in infants is also not further checked to rule out the possibility of neonatal jaundice caused by ABO blood group incompatibility.

CONCLUSION

This study concluded that caesarean section method of delivery is associated with neonatal hyperbilirubinemia. Therefore, normal vaginal delivery is recommended for its beneficial effect both for mothers and newborns.

REFERENCE

Fanaroff AAM, Fanaroff RJAA, Martin RJ. Neonatal-perinatal medicine: diseases of teh fetrus and infant. Missouri: Mosby; 2002. 1123–1134 p.

Ansong-Assoku B, Shah S, Adnan M, Ankola P. Neonatal jaundice [Internet]. StatPearls Internet. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532930/#_NBK532930_pubdet_

Bartlett M, Gourley GR. Neonatal jaundice and disorders of bilirubin metabolism. In: Liver Disease in Children, Fourth Edition. Cambridge University Press; 2011. p. 177–98.

Brits H, Adendorff J, Huisamen D, Beukes D, Botha K, Herbst H, et al. The prevalence of neonatal jaundice and risk factors in healthy term neonates at National District Hospital in Bloemfontein. Afr J Prim Health Care Fam Med. 2018;10(1):1–6.

Anand P, Mangalabharathi S, Aparna C, Gopalakrishnan S, Sachdeva A, Sahoo T, et al. Screening, Prevention, and Management of Neonatal Hyperbilirubinemia. Journal of Neonatology. 2020 Sep 1;34(3):153–69.

Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment ABSTRACT [Internet]. 2017. Available from: http://barnacle.e

Boskabadi H, Rakhshanizadeh F, Moradi A, Zakerihamidi M. Risk Factors and causes of neonatal hyperbilirubinemia: a systematic review study. J Pediatr Rev. 2020;8(4):211–22.

Tavakolizadeh R, Izadi A, Seirafi G, Khedmat L, Mojtahedi SY. Maternal risk factors for neonatal jaundice: a hospital-based cross-sectional study in Tehra. Eur J Transl Myol. 2018;28(3):257–64

Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in Neonates: Types, Causes, Clinical Examinations, Preventive Measures and Treatments: A Narrative Review Article [Internet]. Vol. 45, Iran J Public Health. 2016. Available from: http://ijph.tums.ac.ir

Cherepnalkovski AP, Aluloska NN, Zdraveska N, Piperkova K, Krzelj V. Neonatal Hyperbilirubinemia in Newborns of the Republic of North Macedonia [Internet]. Available from: www.intechopen.com

Menteri Kesehatan Republik Indonesia. KEPUTUSAN MENTERI KESEHATAN REPUBLIK INDONESIA TENTANG PEDOMAN NASIONAL PELAYANAN KEDOKTERAN TATA LAKSANA HIPERBILIRUBINEMIA. Jakarta; 2019.

Sukadi A. Hiperbilirubinemia. Pertama. IDAI, editor. Jakarta.

Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. Vol. 2, The Lancet Child and Adolescent Health. Elsevier B.V.; 2018. p. 610–20.

Slusher TM, Zamora TG, Appiah D, Stanke JU, Strand MA, Lee BW, et al. Burden of severe neonatal jaundice: A systematic review and meta-analysis. BMJ Paediatr Open. 2017 Dec 1;1(1):e000105.

Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F, et al. Neonatal hyperbilirubinemia and rhesus disease of the newborn: Incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res. 2013 Dec;74(SUPPL. 1):86–100.

Shapiro S, le Pichon JB, Riordan SM, Watchkoe J. The Neurological Sequelae of Neonatal Hyperbilirubinemia: Definitions, Diagnosis and Treatment of the Kernicterus Spectrum Disorders (KSDs). Curr Pediatr Rev. 2017 Aug 17;13.

Porter ML, Dennis BL. Hyperbilirubinemia in the Term Newborn [Internet]. Vol. 15, FEBRUARY. 2002. Available from: www.aafp.org/afpAMERICANFAMILYPHYSICIAN599

Fundora J. Hematologic diseases. In: Hughes HK, Kahl LK, editors. The Harriet Lane handbook. 21st ed. St. Louis: Mosby; 2018. p. 504–7.

Maisels MJ. Neonatal jaundice. Pediatr Rev. 2006 Dec;27(12):443– 54.

Shihab RAS, Samman AMB, Aqeel FA, Ghabrah ZT. Difference between breast milk jaundice and breast feeding jaundice: literature review. Int J Community Med Public Health. 2021;8(5):2559.

Gartner LM, Jaundice B. Breastfeeding and Jaundice [Internet]. Available from: www.nature.com/jp

Bratton S, Cantu RM, Stern M. Breast Milk Jaundice. StatPearls Publishing. 2021 Jan.

Moiz B, Nasir A, Khan SA, Kherani SA, Qadir M. Neonatal Hyperbilirubinemia in infants with G6PD c.563C > T Variant. BMC Pediatr. 2012;12(126):1–8.

Gibson M. Neonatal jaundice primary prevention. Wikipedia. 2020.

Kalakonda A, Jenkins B, John S. Physiology, bilirubin [Internet]. StatPearls Internet. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470290/#_NBK470290_pubdet_

Gourley GR. Neonatal jaundice and disorders of bilirubin metabolism. In: Liver Disease in Children, Third Edition. Cambridge University Press; 2007. p. 270–309.

Jeffrey Maisels M. Neonatal Jaundice [Internet]. Vol. 27, Article neonatology Pediatrics in Review. 2006. Available from: http://pedsinreview.aappublications.org/Downloadedfrom 99. Pandey N, Gupta S, Yadav RK, Sarvottam K. PHYSIOLOGICAL JAUNDICE: ROLE IN OXIDATIVE STRESS. ROLE IN OXIDATIVE STRESS Int J Cur Res Rev. 2013.

Wang X, Chowdhury JR, Chowdhury NR. Bilirubin metabolism: Applied physiology. Current Paediatrics. 2006;16(1):70–4.

Cinical practice. Bilirubin in the newborn: Physiology and pathophysiology. Br J Midwifery. 2018;26(6):362–70.

Yaworski A, Meer AV, Wong E. Neonatal Hyperbilirubinemia. McMaster Pathophysiology review. 2018;

AMERICAN ACADEMY OF PEDIATRICS CLINICAL PRACTICE GUIDELINE Subcommittee on Hyperbilirubinemia Management of Hyperbilirubinemia in the Newborn Infant 35 or

More Weeks of Gestation [Internet]. 2004. Available from: www.aap.org/family/jaundicefaq.

Chambers B, Mack C. Neonatal hyperbilirubinemia. In: Berman's pediatric decision making. 5th ed. Philadelphia, CA: Elsevier; 2011. p. 288–91.

Stark A, Bhutani V. Neonatal Hyperbilirubinemia. In: Manual of neonatal care. 8th ed. Philadelphia: Lippincott Williams & Wilkins (LWW); 2016. p. 336–52.

Boskabadi H, Ashrafzadeh F, Azarkish F, Khakshour A, Author C. P:7-13 Complications of Neonatal Jaundice and the Predisposing Factors in Newborns. J Babol Univ Med Sci. 2015;17(9):7–13.

Nakanga W, Patel P, Panjwani S, Kennedy N, Kawaza K. Supra-treatment threshold neonatal jaundice: Incidence in HIV-exposed compared to non-exposed neonates at Queen Elizabeth Central Hospital in Blantyre, Malawi. Malawi Med J 2015; 27(3): 104- 108. doi: 10.4314/mmj.v27i3.7.

Tamook A, Salehzadeh F, Aminisani N, Moghaddam yeganeh G. Etiology of Neonatal Hyperbilirubinemia at Ardabil Sabalan Hospital, 2003. J Ardabil Univ Med Sci 2005; 5(4): 316-320.

Kristin M, Henry T. Neonatal Jaundice: Strategies to reduce bilirubin induced complications. Postgraduatea Medicine 1999; 106(6): 112-115. doi: 10.3810/pgm. 1999.11.775

Jui-Hsing Chang, Chin-Yuan Hsu, Joan C, Chie-Pein Chen, Fu-Yuan Huang, Suchuan YU. Comparative analysis of neonatal morbidity for vaginal and caesarean section deliveries using hospital charge. Acta Pediatric 2006; 95: 1561-1566. doi: 10.1080/08035250600711066

Sharifizad M, Khodakaram N, Jannesari S, Akbarzadeh A. The Outcomes of Natural Childbirth and C-Section on the Mother and Infant's Health in Selected Hospitals in Tehran. Horizon Med Sci 2012; 18(1): 5-11.

Esmailepour-Zanjani S, Safavi M, Jalali S, Abyane E E. Incidence and associated factors of neonatal hyperbilirubinemia at Hedayat hospital. J Shahid Beheshti Sch Nurs Midwifery 2007; 17(59): 19-25. 21. Osbern L M, Reiff M I, Bolus R. Jaundice in full term neonates. Pediatrics 1984; 73(4): 520-526.

Naghipour Ali, Gharebaghi Mostafa, Fadaee Mannouchehr et al. The study of association of delivery mode on neonatal jaundice in Al-zahra and Children's hospital of Tabriz in the first 6 motnhs of 1395: cross sectional; 2018. Med. Journal of Tabriz University of Medical Sciences and Health Services, March 41(6): 83-90.

Ozkan S, Caliskan E, Doger E, Yucesoy I, Ozeren S, Vural B. Comparative efficacy and safety of vaginal misoprostol versus dinoprostone vaginal insert in labor induction at term: a randomized trial. Arch Gynecol Obstet. 2009; 280(1):19-24.

Engle WA, Tomashek KM, Wallman C. Committee on fetus and newborn, American academy of pediatrics. "Late-preterm" infants: a population at risk. Pediatrics. 2007; 120(6):1390-401

Chang PF, Lin YC, Liu K, Yeh SJ, Ni YH. Risk of hyperbilirubinemia in breast-fed infants. J Pediatr. 2011; 159(4):561-5.

Davies DP, Gomersall R, Robertson R, Gary OP, Turnubll AC. Neonatal jaundice and maternal oxytocin infusion. Br Med J. 1973; 3(5878):476-7.

Agarwal V, Singh V, Goel SP, Gupta B. Maternal and neonatal factors affecting physiological

jaundice in western U.P. Ind J physiol pharmacol. 2007; 51(2):203-6.
Sharifizad M, Khodakarami N, Jannesari S, Akbarzadeh A. The outcomes of natural childbirth and C-section on the mother and infant's health in selected hospitals in Tehran. Ofogh-e-Danesh. 2012; 18(1):5-11 (Persian).
Qhaemi S, Kasaeian AM. Evaluation effect of oxytocin to induce labor on neonatal hyperbilirubinemia. J Isfahan Med Sch. 2000; 18(58):35-8.
Ehsan Garosi, Mohmammadi Fatemeh, Ranjkesh Fatemeh. The Relationship between Neonatal Jaundice and Maternal and Neonatal Factors. Qazvin University of Medical Sciences Iran, 2008.