



## Neonatal Jaundice Causal Factors: A Literature Review

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### ABSTRACT

**Background:** Jaundice (neonatal icterus), known as yellowish baby is a condition where the yellowing of the skin and sclera in newborns, due to increased levels of bilirubin in the blood (hyperbilirubinemia) which subsequently causes an increase in bilirubin in the fluid outside the cell (extracellular fluid). Jaundice is one of the contributors to infant morbidity in Indonesia because it can cause the baby's body to become limp, unwilling to suck, increased muscle tone, stiff neck, muscle spasms, convulsions, sensory disturbances, mental retardation, disability, and even death.

**Objective:** This study aimed to review the evidence related to the factors causing jaundice in neonates.

**Method:** This research method was a literature review study. Journal searches were carried out by applying online database such as ScienceDirect and PubMed. Author also used google scholar for search engine. The inclusion criteria in this study were journals published in 2015-2020 using Indonesian and English and full text. Journal search results obtained as many as 10 journals were reviewed in this study.

**Results:** Birth weight of the baby, gestational age, asphyxia, infection, length of labor, frequency and sex are factors that cause jaundice while primiparous mothers are factors that do not cause jaundice. Based on the results of the review of the article the researchers found that there were gaps in the study this is research on the factors causing the occurrence of jaundice more focused on health problems of birth weight of the baby, gestational age, asphyxia, and infection, duration of delivery, frequency and sex. Only few researches are examining the factors associated with factors causing jaundice in neonates.

**Conclusion:** The factors causing the occurrence neonatal jaundice are more focused on health problems of birth weight of babies, gestational age, asphyxia, infection, length of labor, frequency and sex. There are still few studies that examine the factors associated with factors that cause jaundice in neonates.

**Keywords:** *Mother factor, Baby factor, Jaundice, Neonatal Icterus*

## **BACKGROUND**

Infant Mortality Rate (IMR) in Indonesia reaches 22 per 1000 live births, while the Under-five Mortality Rate (AKBA) reaches 26 per 1000 live births. In this country, IMR is caused by asphyxia (37%), prematurity (34%), sepsis (12%), hypothermia (7%), jaundice (5%), post-maturity (3%), and congenital abnormalities (1%) (SUPAS, 2015). Jaundice is not the highest cause of IMR but it becomes one of the contributors to infant morbidity in Indonesia as it can weaken the baby's condition and causes problems with sucking, increase muscle tone, stiff neck, muscle spasms, seizures, sensory disturbances, mental retardation, disability, and even death (Amandito et al., 2018).

Jaundice or icterus neonatorum or commonly known as yellow discoloration of the body tissue in newborns due to the increased levels of hyperbilirubinemia which then causes an increase in bilirubin in the extracellular fluid (Govoni et al., 2019). Factors causing jaundice in neonates are race, rhesus disease, ABO incompatibility, maternal age, social class, primipara, family history of jaundice, low birth weight (LBW), premature, and inadequate breastfeeding (Kyu et al., 2018; Olusanya et al., 2015). Increased levels of bilirubin in newborns are a normal transitional phase, but excessively increased levels in the blood can cause kernicterus, which requires special treatment because if left untreated it will cause death (Tani & Castagna, 2017).

Midwives as health workers have the authority to prevent or early detect pathological jaundice by providing health education to pregnant women regarding nutritional needs and the importance of exclusive breastfeeding. Midwives have the role to provide counseling to mothers about signs or symptoms of jaundice and home care such as giving enough breast milk and sunbathing the baby in the morning. Then, if there is no improvement, the mother should take the baby to a health facility (Maryunani, 2013).

One of the causes of jaundice is late feeding. Late feeding is the delay in feeding the neonate, especially in premature babies, which leads to an increase in the intensity of physiological jaundice. Babies of mothers with low breast milk production or mothers who are still in the intensive care unit (birth delivery with Sectio Caesarea) do not get colostrum immediately. Babies who don't get colostrum have excess bilirubin which can't be excreted so the baby experiences jaundice. Colostrum is believed to have a laxative effect to help release the first feces due to excess bilirubin (Otsuka et al., 2008). The community considers jaundice a dangerous disease indicated by the fact that mothers always ask whether their newborn baby experience jaundice or not. Mothers with babies who have jaundice feel anxious because jaundice requires special attention and care as it can lead to death. One of the policies that have been proven to increase the proxy indicators (birth delivery assisted by health personnel) to reduce MMR and IMR is the Birth Planning and Complication Prevention Program (P4K). Besides, this P4K program encourages pregnant women to have antenatal care, birth delivery, post-natal care, and newborn care at health facilities assisted by skilled. Postpartum mothers are encouraged to practice Early Breastfeeding Initiation (IMD) and exclusive breastfeeding for 6 months (Ministry of Health, 2013).

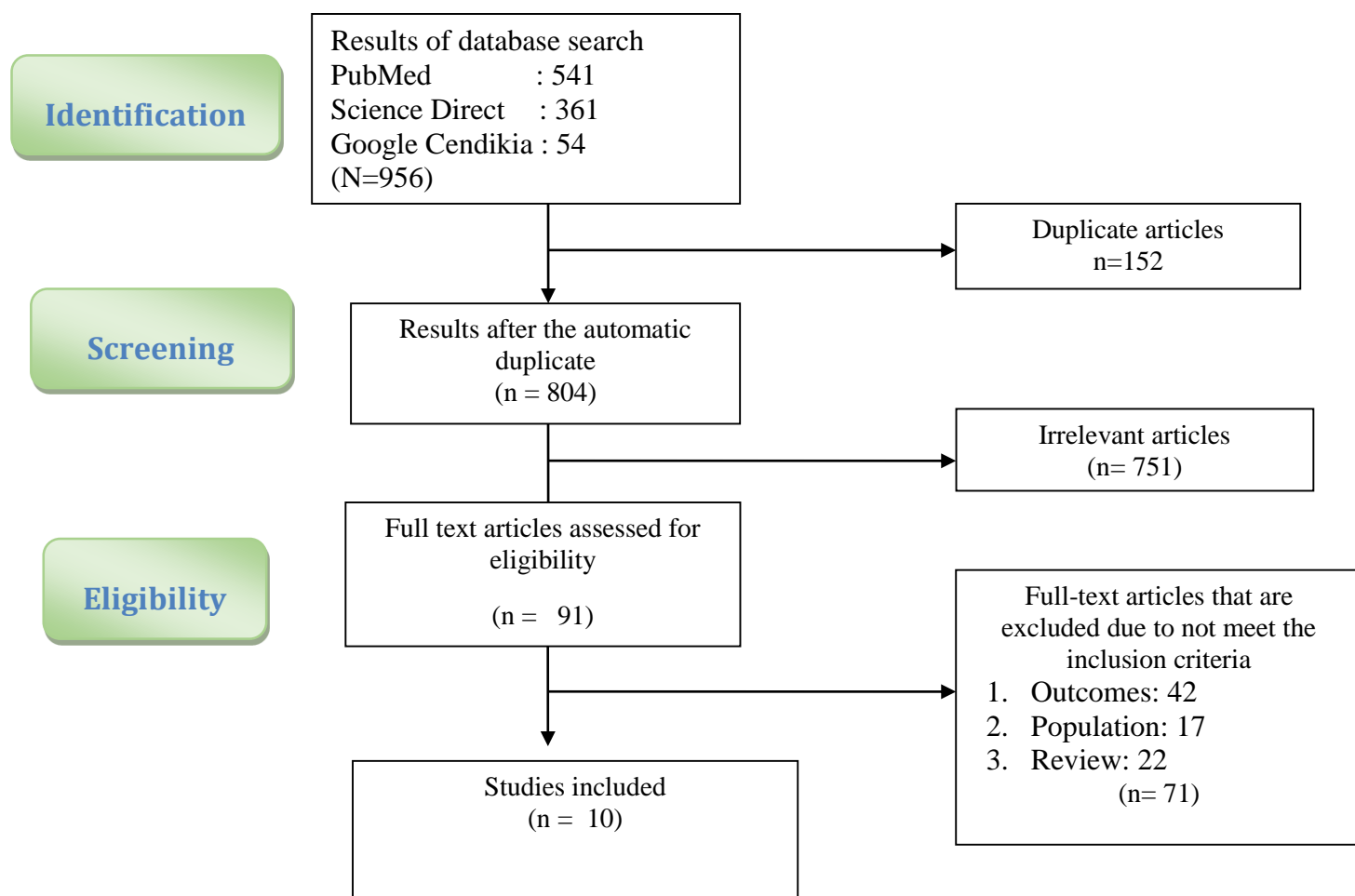
## **OBJECTIVE**

This study was aimed to review the evidence related to the factors causing jaundice in neonates.

## METHODS

This study was a literature review that is conducted by collecting library data to solve a problem based on critical analysis and in-depth knowledge of relevant library materials (Anwar et al., 2015; Rahman et al., 2018). This literature review used narrative review. A narrative review is research compiling eligible sources to get a summary of the latest relevant theories and empirical findings (Cisco, 2014). The steps in this narrative review are as follows: (1) Identify narrative review questions, (2). Identifying relevant articles, (3). Article selection, (4). Charting Data, and (5). Compile, summarize and report results (Arksey & O'Malley, 2015).

In this literature review, the authors include inclusion criteria such as the maximum time span for publishing articles in the last 5 years, using English and Indonesian, the subject is neonates, the type of original article and the theme of the contents of the article are factors that cause neonatal jaundice.



## RESULTS

Birth weight of the baby, gestational age, asphyxia, infection, length of labor, frequency and sex are factors that cause jaundice while primiparous mothers are factors that do not cause jaundice. Based on the results of the review of the article the researchers found that there were gaps in the study this is research on the factors causing the occurrence of jaundice more focused on health problems of birth weight of the baby, gestational age, asphyxia, and infection, duration of delivery, frequency and sex. Only few researches are examining the factors associated with factors causing jaundice in neonates.

No	Title/Author/ Year	Country	Objective	Method	Result
1.	Factors Causing Neonatal Jaundice in the NICU Room at Arifin Achmad Hospital, Riau Province/ Febrianti Maharani/ 2016.	Indonesia	To identify factors causing neonatal jaundice in the NICU room at Arifin Achmad hospital, Riau Province in 2016.	Quantitative study with descriptive design. Checklist sheets and secondary data. The population is all data on jaundice in newborns in the NICU room at Arifin Achmad Hospital, Riau Province with a total of 46 cases and 46 samples	Of the total 46 samples, the majority of LBW <2500 gr were 26 people (56.5%), Premature Infants <37 weeks reached 18 people (39.1%) and the breastfeeding factor was 2 people (4.4%). These results are expected as input for agencies to improve their efforts to provide bucket c services and light therapy for jaundice babies.
2.	The Relationship between Perinatal and Neonatal Factors on the Incidence of Neonatal Jaundice / Dwi Yuliawati,	Indonesia	To determine the relationship between perinatal and neonatal factors on the incidence	A correlation study with a retrospective cohort design. Using simple random sampling technique.	The results showed that there was a relationship between birth weight (p= 0.018; POR 0.085 95% CI 0.10-0.713), gestational age (p= 0.044; POR= 0.202 95% CI 0.049-0.836), and perinatal complications (p= 0.031; POR = 4.714 95% CI 1.250-17.784).

	Reni Yuli Astutik / 2018		of neonatal jaundice at Kediri District Hospital	The population in this study were all infants with jaundice at Kediri District Hospital in January - December 2016 with a total of 61 infants. The sample was 54 respondents.	on the incidence of neonatal jaundice and there was no relationship between gender ( $p = 0.441$ ; $POR = 0.503$ 95% $CI 0.143-1.767$ ) and the incidence of neonatal jaundice in Kediri District Hospital. It is maybe due to other factors. LBW conditions, prematurity, male sex, perinatal complications (asphyxia/sepsis/cephalhematoma) lead to the occurrence of pathological jaundice in infants.
3.	The Effect of Low Birth Weight on the Neonatal Jaundice Incidence in Sidoarjo/ Ndaru Puspita/ 2018	Indonesia	To identify the effect of LBW on the incidence of neonatal jaundice at Sidoarjo Hospital.	Cross sectional study. Using simple random sampling technique. The population was all newborns in the neonatal room at Sidoarjo Hospital with a total of 190 infants. The sample was determined using the Slovin formula obtaining 129 samples.	This study showed that the incidence of LBW was 21.71% and the incidence of neonatal jaundice was 29.46%. LBW babies who experienced neonatal jaundice reached 17.80%. The results of the chi square analysis obtained a value of $p = 0.01$ ( $p < 0.05$ ) which means that LBW influences the incidence of neonatal jaundice at Sidoarjo Hospital.
4.	Factors Associated with Jaundice	Indonesia	To identify factors	A cross sectional study. Using	The results of the chi square test showed a relationship between

	in Neonates/Siti Rohani, Rini Wahyuni/2017		associate with the incidence of jaundice in neonates.	a systematic random sampling technique. The population was 1041 neonates with the sample of 196 neonates.	birth weight (p-value 0.000 <0.05), OR= 3.084, and gestational age ((p was related to infection (p-value 0.005 <0.05), OR= 2.444, asphyxia (p has no relationship to the type of delivery (p multiple bucket c regression). The gestational age was the most dominantly related to the incidence of jaundice in neonates (p-value 0.000), OR = 4.698. At least 4 visits of EFA to pregnant women can prevent infection.
5.	Prevalence of and mothers' knowledge, attitude and practice towards glucose-6-phosphate dehydrogenase deficiency among neonates with jaundice: a cross-sectional study/ Zeinab A Kasemy, Wael A Bahbah, Sally M El Hefnawy, Safa H Alkalash/2019	Mesir	To estimate the prevalence of G6PD deficiency among neonates with jaundice and to assess maternal perceptions of G6PD and NNJ.	A cross-sectional study. The data collected covered the characteristics of mothers and newborns. Laboratory investigations included serum bilirubin, reticulocyte count, ABO grouping, Rh typing and neonatal serum G6PD test. Mothers were interviewed individually using a structured questionnair	The prevalence of G6PD deficiency reached 10.10%. Neonates with G6PD deficiency showed higher serum bilirubin levels (p < 0.001). Male gender, family history of G6PD deficiency and relatives become risk factors for G6PD deficiency (OR = 4.27, 95% CI 1.66 – 10.99; OR = 9.54, 95% CI 4.80-18.95; OR = 10.219, 95% CI 5.39 – 19.33, respectively). Mothers' perceptions about NNJ and G6PD were low, namely 30% for MNJ and 17.10% for G6PD. Respondents have a positive attitude towards NNJ (46.8%) and G6PD deficiency (45.0%), with a good practice of NNJ (29.9% ) and G6PD deficiency (19.9%).

				e to assess their perceptions of G6PD deficiency and NNJ. 487 neonates with indirect hyperbilirubinemia from June 2018 to July 2019 in Egypt	
6.	Knowledge Level and Determinants of Neonatal Jaundice: A Cross-Sectional Study in the Effutu Municipality of Ghana/ Prince Adoba, Richard K.D.Ephraim, Kate Adomakowaah Kontor, Joseph-Josiah Bentsil, Patrick Adu, Maxwell Anderson, Samuel Asamoah Sakyi, and Paul Nsiah/2018	Ghana	To identify factors associated with neonatal jaundice and assess the level of knowledge of mothers about this condition	A case control study with a cross-sectional design. Using a well-structured questionnaire to collect maternal and child histories data. One hundred and fifty (150) neonates consisting of 100 with clinically proven jaundice and 50 without jaundice in Trauma and Specialist Hospital in Effutu City were involved in this study	The majority of the respondent (54%) born together had a pregnancy 1 – 3 days after birth with 10% with a postpartum period. Duration of labor and pregnancy at birth with body weight <0.05). G6PD abnormalities were found in 11 (12%) neonates with jaundice and ABO incompatibility was found in 18%. neonates born to mothers with formal employment and those who had a long labor were significantly more likely to have neonatal jaundice (OR = 4.174, <i>P</i> = 0.003; OR = 2.389, <i>P</i> = 0.025, resp.). more likely to develop neonatal jaundice (OR = 2.347, <i>P</i> = 0.044). Only 17.3% of mothers had heard of neonatal jaundice. School becomes the main source of information formation about neonatal jaundice (34.6%). The majority of

					participants did not know that NNJ can cause damage to other organs in the body (90%).
7.	Meconium microbiome associates with the development of neonatal jaundice/Tian yu dong et all/2018	China	to identify the meconium microbiome in newborns and to check its association with risk of neonatal jaundice.	A case control study The population was taken from the NMU Mother and Child Cohort Study (Phase II), a prospective cohort designed to study prenatal risk factors on pregnancy outcomes and child health. Participants in this study were mother-infant pairs recruited in early pregnancy from hospitals affiliated with Nanjing Medical University between February 2014 and November 2015. 301 newborns	The logistic regression model showed that higher variability was significantly associated with a lower risk of jaundice in babies born by cesarean section (OR 0.72, 95% CI 0.52-0.98), but not in babies born spontaneously. A relative abundance of Biobobobium pseudolongum in newborn meconium was significantly associated with a lower risk of jaundice both in infants born by cesarean section and in total subjects (OR 0.24, 95% CI 0.07–0 .68; OR 0.55, 95% CI 0.31-0.95, respectively). Spearman's correlation showed that the relative abundance of B. Pseudolongum was significantly correlated with $\alpha$ -diversity (P < 0.01).



				with meconium samples from 2014 to 2015.	
8.	Breastfeeding during breast milk jaundice – a pathophysiological perspective/  Prameela Kannan Kutty, FRCP (Edin), FRCPCH (UK)/2019	Malaysia	To identify whether breastfeeding affects the incidence of jaundice.	Literature review. Reviewing the literature and integrating relevant information concerning neonatal jaundice, entry of bilirubin into the immature brain and how breastfeeding affect neonatal jaundice	Some substances in breast milk may be responsible for jaundice but continuous breastfeeding provides many benefits. Breastfed infants benefit from fewer infections, increased organ and physiological maturation, and the prospect of genetic modification of certain diseases. This beneficial measure may also reduce the risk of early jaundice and its complications. The holistic integration of knowledge clarifies the overall benefits of continues breastfeeding. Breastfeeding jaundice may reflect a holistic expression of tissue protection and increased neonatal survival
9.	Indirect neonatal hyperbilirubinemia in hospitalized neonates on the Thai-Myanmar border: a review of neonatal	Thailand	To describe neonates with INH, the burden of severe INH and factors associated with severity in resource-	Retrospective evaluation of anonymized records of neonates treated at the Thai-Myanmar border. Anonymized records of neonates	A total of 2980 records were reviewed and found that 1580 (53%) had INH within the first 14 days of life. INH was moderate in 87% (1368/1580) and severe in 13% (212/1580). From 2009 to 2011, the proportion of severe INH decreased from 37% to 15% and mortality declined from 10%

	medical records from 2009 to 2014/ L. Thielemans et al/2018		limited setting	treated at the Thai-Myanmar border	(8/82) to 2% (7/449) with the adoption of standard guidelines and light-emitting diode (LED) phototherapy. Severe INH is associated with: prematurity (<32 weeks), Adjusted Odds Ratio (AOR) 3.3; 95% CI 1.6-6.6 and 32 to 37 weeks, AOR 2.2; 95% CI 1.6-3.1), Glucose-6-phosphate dehydrogenase deficiency (G6PD) (AOR 2.3; 95% CI 1.6-3.3.3), potential ABO mismatch (AOR 1.5; 95% CI 1.0-2.2) and late presentation (AOR 1.8; 95% CI 1.3-2.6). The risk of developing severe INH and INH-related mortality increases significantly with each additional risk factor.
10.	Relationship between Neonatal Skin Bilirubin Level and Severe Jaundice with Maternal, Childbirth, and Neonatal Characteristics / Robabe Seyedi et al/2019	Iran	to test for various maternal, labor, and neonatal factors affecting neonatal skin bilirubin levels and severe jaundice	A cross-sectional study. Using a convenience sampling technique. This study involved 1066 healthy neonates with gestational age of 35 weeks or more and birth weight of $\geq 2000$ g at Alzahra and	Of the total neonates followed up, 94 (9.96%) cases developed severe jaundice and 850 (90.04%) newborns did not show any symptoms of this complication. The adjusted general linear model results showed that the infant's bilirubin level was significantly correlated with a history of jaundice in previous children, the infant's age at first meconium excretion, the frequency of feedings, the gestational age, the mother's blood type, and the number of maternal ultrasounds check during

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Taleghani hospitals in Tabriz, Iran, during 2016-2017. Data were collected using a three-part questionnaire that assessed maternal, childbirth and neonatal characteristics based on the medical history of the mother and newborn and interviews with the mother.	pregnancy. Besides, the adjusted logistic regression results revealed an association between severe jaundice and variables like residence, history of jaundice in previous children, feeding the infant with water or sugar water during the feeding interval, frequency of feeding the infant, gestational age, mother's blood type, time of discharge from hospital, and number of pregnancies.
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## DISCUSSION

### 1. Factors associated with jaundice

#### a. Babies with low birth weight associated with jaundice

Babies with low birth weight have a higher risk of infection because of decreased maternal immunoglobulin reserves, impaired ability to form antibodies, and damaged integumentary system (thin skin and weak capillaries). Hypoglycemia in premature infants and those with growth disorder have lower glycogen stores so they cannot mobilize glucose as fast as normal-term babies. Premature babies have immature hormone and enzyme responses. Hyperbilirubin is also caused by hepatic maturity factors so the indirect bilirubin conjugation to direct bilirubin has not been perfect. Jaundice can be worsened by polycythemia, hemolysis bruises, and infection as hyperbilirubin can cause kernicterus so that the baby's skin color and bilirubin must be frequently recorded and checked if it appears early or turns to brown faster (Thielemans et al., 2018; Yuliawati & Astutik, 2018).

#### b. Gestational age associated with jaundice

Jaundice is more common in premature babies and babies with low birth weight. This is in line with (Yuliawati & Astutik, 2018) that there is a relationship between gestational age and the incidence of jaundice in newborns. (Puspita, 2018; Seyedi et al., 2019) explains that the gestation period is the most dominant aspect of the incidence of jaundice. This means that gestational age is a risk factor for the incidence of hyperbilirubin in newborns as gestational age is an important factor that determines the health of the baby. Early-term babies are associated with low birth weight which can affect the baby's immune system which is not ready to accept and adapt to the environment outside so they have the potential for various complications including jaundice.

c. Asphyxia associated with jaundice

This is in line with the results of a previous study by (Mubasyiroh et al., 2017) that there is a relationship between asphyxia and jaundice. Asphyxia is caused by impaired oxygen transport during pregnancy or childbirth. If this continues, it can cause anaerobic metabolism in the form of glycolysis of body glycogen resulting in the reduction in glycogen in the liver which leads to jaundice (Dong et al., 2018; Septianingrum & Yasintha, 2018) reveals that there is a relationship between asphyxia and jaundice. Babies with asphyxia have a risk of 2.88 times experiencing physiological jaundice. This hypoxia is associated with factors emerging in pregnancy, childbirth, or post-partum. The impact of asphyxia will be worse without proper handling. Actions are taken to maintain the baby's survival and limit possible further symptoms.

d. Infection associated with jaundice

This is supported by (Olusanya et al., 2015) that congenital infections can affect the intrahepatic or extrahepatic portal vein which will cause an increase in bilirubin leading to jaundice. The infected babies may have mild conjugated hyperbilirubinemia. Another stigma of congenital infection may be involved especially, in the case of bacterial infection which leads to elevated bilirubin levels. The use of antibiotics and influenza drugs can cause liver dysfunction in babies so that the baby's liver cannot optimally dissolve bilirubin into the water to be transported into bile and excreted into the intestine to become urobilinogen. This causes an increase in the level of bilirubin in the plasma resulting in jaundice.

Length of Labor and Jaundice Incidence. Jaundice is not only caused by the baby factor but also the length of the labor. G6PD abnormalities were found in 11 (12%) neonates with jaundice and ABO incompatibility (18%). Babies born to mothers with formal employment and prolonged labor were significantly more likely to have jaundice (OR = 4.174,  $P = 0.003$ ; OR = 2.389,  $P = 0.025$ , respectively) and more likely to develop jaundice (OR = 2.347,  $P = 0.044$ ). Only 17.3% of mothers had heard of jaundice.

Prolonged labor is caused by wrong pushing, premature rupture of membranes, fetal factors, abnormalities and a narrow pelvis (Nuraeni et al., 2018).

e. Gender associated with jaundice

The results of this study indicate that gender is related to the incidence of jaundice because baby boys have a higher risk of jaundice than baby girls due to some factors, such as the prevalence of Gilbert's syndrome (a genetic disorder of bilirubin conjugations) which is reported higher than in girls and a deficiency of

G6PD which is the most common disorder of enzyme and is associated with sex chromosomes (x-linked) which generally manifests in males only (Battersby et al., 2018).

f. Mother's knowledge related to the incidence of jaundice

The results in this study that maternal knowledge is related to the incidence of icterus because low maternal knowledge about neonatal jaundice can cause a very large risk to ignore predisposing factors that might be avoided and even signs that require immediate jaundice treatment in newborns make them develop jaundice and are often admitted to health facilities when irreversible neurotoxicity and brain damage may have occurred (Hashim et al., 2020).

g. Meconium bacteria are associated with jaundice

The results of this study that meconium microbes are associated with the incidence of jaundice only applies to cesarean delivery due to delays in early breastfeeding (Fox et al., 2015; Kutty, 2019). The study also explained that bacteria in the gut have an important role in mediating bilirubin in neonates.

2. Factors that are not associated with jaundice

a. Primipara mothers are not associated with jaundice

Primipara mothers do not cause jaundice. This is explained in the third article that the incidence of low birth weight and jaundice reach 21.71% and 29.46% respectively. Babies with low birth weight who has jaundice reach 17.80%. The results of the chi-square analysis obtained a p-value of = 0.01 ( $p < 0.05$ ) which means that low birth weight influences the incidence of jaundice at Sidoarjo Hospital.

b. Types of birth delivery is not associated with jaundice

The type of birth delivery does not cause jaundice. This is explained in the 4th article that the chi-square test showed that there was a relationship between birth weight ( $p$ -value  $0.000 < 0.05$ ), OR = 3.084, gestational age ( $p$  relationship with infection ( $p$ -value  $0.005 < 0, 05$ ), OR = 2.444, and asphyxia ( $p$  no relationship with the type of delivery ( $p$  multiple logistic regression showed that the gestational age variable is the most dominantly associated with jaundice ( $p$ -value 0.000), OR = 4.698. At least 4 times PUS visits to pregnant women can prevent infection. Babies born by vacuum and forceps extraction have a tendency to have closed bleeding in the head, such as caput succedaneum and cephalohematoma which are risk factors for hyperbilirubinemia in jaundice. However, not all birth deliveries experience jaundice (Damarini et al., 2013).

The statistical tests showed no relationship but this study indicated that Section Cesarean and vacuum extraction causes the risk of pathological jaundice. There was no relationship in this study because the incidence of jaundice is caused by many factors, including uncontrolled factors. Control factors cover prematurity, infection and cephal haematoma, while uncontrolled factors cover asphyxia, hypoalbuminemia, diabetes mellitus in mothers and breast milk jaundice.

## CONCLUSION

Infant birth weight, gestational age, asphyxia, infection, length of labor, frequency, mother's knowledge, meconium microbe and gender are factors that cause jaundice, while mothers with primiparous status are factors that do not cause jaundice. Based on the results of the review of the articles, the researchers found gaps in this study, namely:

- a. Research on the causes of jaundice has focused more on health problems at birth weight, gestational age, asphyxia, infection, length of labor, frequency, mother's knowledge, meconium microbe and gender.
- b. There are still few studies that examine the factors associated with the factors that cause jaundice in neonates.

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