Turnitin Association between birth route and neonatal sepsis manuscript

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Association Between Birth Route with Early and Late-Onset Neonatal Sepsis in Term Infants: A Case-Control Study in NICU of a Tertiary Hospital in East Java, Indonesia

Abstract

Background: In 2020, neonatal sepsis was reported amongst the leading causes of neonatal death. The birth route can affect the variety of microbial flora in neonates. Microbial colonization through the birth canal is vital in reducing susceptibility to infection. This study aims to identify the association between birth route with early and late-onset neonatal sepsis in term infants.

Method: Hospital-based case-control study was performed in term infants diagnosed with neonatal sepsis at the NICU of a tertiary referral hospital in East Java between 1 January 2019 – 31 December 2019. Preterm neonates were excluded as they may contribute to neonatal sepsis. Chi-square test and an odds ratio (OR) with a 95% confidence interval (95% CI) were used to analyse the obtained data. P-value <0.05 was considered statistically significant.

Results: From the 54 neonatal sepsis patients recruited, a majority were early-onset sepsis (63.0%) and born via cesarean section (66.7%). A significant association between birth route with neonatal sepsis onset (p=0.046) was found. However, no significant association was found between birth route with neonatal sepsis (p=0.321). Term infants born via cesarean section had a 3.25 times higher risk (95% CI 1.00 – 10. 60) of early-onset neonatal sepsis than vaginal delivery.

Conclusions: Delivery by cesarean section can increase the risk of developing early-onset neonatal sepsis in term infants.

Keywords: Cesarean section, neonatal sepsis, term infants, vaginal delivery.

Introduction

The key indicator of neonatal health and well-being is the neonatal mortality rate. This number has developed into the major component of the under-five mortality rate in recent years (1). In 2020, 71.97% of under-five deaths in Indonesia occurred in the neonatal period. East Java is one of the provinces in Indonesia that has the highest neonatal mortality rate. It reached around 80% of under-five mortality in 2017– 2020. In 2020, Indonesia's leading causes of neonatal death were low birth weight 35.2%, asphyxia 27.4%, congenital abnormalities 11.4%, and sepsis 3.4% (2). Meanwhile, Dr.Soetomo Hospital, a tertiary referral hospital in East Java, reported that from 101 neonatal deaths between September– February 2015, sepsis was found in 44.4% of early and 68.4% of advanced neonatal deaths (3).

Neonatal sepsis is a systemic illness originating from a bacterial, viral, or fungal infection in infants at the first 28 days of life. The wide range of symptoms and lack of early diagnostic tools present a problem for neonatologists. Early-onset sepsis (EOS) and late-onset sepsis (LOS) are the two classifications of neonatal sepsis depending on the onset of symptoms (4). Potential maternal risk factors of neonatal sepsis include mode of delivery, urinary tract infection, premature rupture of membranes (PROM), intrapartum fever, and chorioamnionitis (5,6).

The birth route can affect the variety and nature of microbial flora in neonates. Early postnatal microbial colonization through the birth canal is vital in reducing susceptibility to infection (7). In a study by Shaw et al the persistence of atypical microbial flora such as *Enterobacteriaceae* and *Staphylococci* was associated with LOS (8). LOS presents a burden in the neonatal intensive care units (NICUs) attributable to an increased tendency of premature infants survival rate, correlated to the advancement of healthcare in recent decades (9). There are still differences regarding the association between birth route and neonatal sepsis until now. Some studies found a significant association, but some concluded otherwise (10– 12). No study has been reported investigating the association between birth route and

neonatal sepsis onset in term infants. Thus, this study aims to identify the association between birth route with EOS and LOS in term infants.

Method

Study Design

This case-control study was carried out from neonates admitted at Dr. Soetomo Hospital, Surabaya, between 1 January 2019 – 31 December 2019. The total number of neonatal sepsis cases in Dr. Soetomo Hospital Surabaya between 1 January 2019 – 31 December 2019 was 242. Of the 242 cases, 161 patients were admitted to the NICU,107 of the 161 patients were born preterm. As a result, after excluding premature neonates, 54 patients were recruited as the case group. Our inclusion criteria for the case group consisted of the following criteria: age 0– 28 days neonates admitted to the NICU of Dr. Soetomo General, term infant born after 37 completed weeks of gestation, diagnosed with neonatal sepsis based on clinical manifestations and laboratory tests assessed by physicians. Clinical features considered in this study were temperature instability (fever ≥38.0° C and hypothermia ≤36.5° C), apneau, tachypneau, chest retraction, nasal flaring, tachychardia, cyanosis, hypotonia, hyporeflexia, and jaundice. The laboratory test components of a sepsis screen include a total leucocyte count of <5000/cumm or >20.000/cumm, an absolute neutrophil count <2 x 109/L, I:T ratio of >0.2 and C-Reactive Protein (CRP) >1mg/L. The exclusion criteria included neonates with incomplete medical record data and/or laboratory results. Preterm neonates defined as infants born before 37 completed weeks of gestation were excluded as they may contribute to neonatal sepsis. The 54 patients of the control group were selected by random sampling from 1478 infants delivered in the obstetrics and gynaecology emergency. Inclusion criteria for the control group were: age < 28 days on admission, a final diagnosis other than neonatal sepsis, admitted the same year as the case group, hospitalized in NICU which is the same ward with the comparing case.

Data collection

Secondary data was collected from the medical record centre of Dr. Soetomo Hospital. Based on the onset of symptoms, neonatal sepsis was categorized into early-onset sepsis (EOS) if it occurred less than 72 hours following birth and late-onset sepsis (LOS) if presented after 72 hours. Mode of delivery was classified based on the birth canal route, namely cesarean section and vaginal delivery

Ethical issues

Ethical clearance was approved and issued by the ethics committee of Dr. Soetomo Hospital, Surabaya, Indonesia (No. 0371/105/XI/2020). Information obtained from patient's medical records gathered during the study is maintained confidential.

Statistical analysis

The acquired data for bivariate analysis was conducted with the chi-square test. P-value < 0.05 was considered as statistically significant. For univariate analysis, mean ± SD was used for continuous data, while frequency with percentages was utilized for categorical data. Calculation of odds ratio (OR) with a 95% confidence interval (95% CI) was used to estimate the magnitude of association. All test was performed using SPSS version 25.0.

Results

As presented in table 1, the mean birth weight of both the case (2571.39 ± 625.837 grams) and control group (2785.19 ± 658.606 grams), both groups were normal birth weight above 2500 grams. The mean gestational age of the case group (38.33 ± 1.149 weeks) was higher than the control (36.67 ± 2.548 weeks). The birth

length of infants was lesser in the case group (43.24 ± 6.318 cm) than (48.78 ± 3.045 cm). A majority of the patient were male in the case group (59.3%). Meanwhile, there were more females (51.9%) than male neonates (48.1%) in the control group. Cesarean section dominated the delivery mode of infants in the case (66.7%) and the control (57.4%). EOS was nearly twice as common (63.0%) than LOS (37.0%). Most neonates had a fifth-minute Apgar score of 7– 10, both in the case (66.7%) and control (94.4%) group.

The findings of the bivariate analysis conducted with chi-square test resulted in a p-value >0.05 (p=0.321), which indicates no significant association between birth route and neonatal sepsis (Table 2). However, as shown in table 3, there was a significant association between the birth route with neonatal sepsis onset in term infants (p=0.046). Term infants born via cesarean section had a 3.25 times higher risk (95% CI 1.00 – 10.60) of early-onset neonatal sepsis than vaginal delivery.

Discussion

Neonates are individuals with immunological immaturity that causes susceptibility to infection. Understanding the risk factors helps early prediction in critical illnesses, such as sepsis (13). The risk factors of neonatal sepsis in the perinatal period cannot be controlled and are challenging to diagnose directly, thus causing high morbidity and mortality (14). Low birth weight (LBW) has been associated as a strong risk factor of developing neonatal sepsis (15). An insufficient maturation of the body's organs and difficulty feeding and digesting breast milk in LBW infants causes a developmental disturbance of the immune system, causing an increased predisposition to infection (16). The mean birth weight of neonatal sepsis patients in this study was normal birth weight infants, contrary to what most studies show. Premature infants were excluded in this study, as a result a majority of low birth weight infants were also excluded.

This study identified the highest incidence of neonatal sepsis in male infants (56.2%). Although higher percentage of male infants was found in neonatal sepsis born via vaginal delivery, there was no significant difference of percentage compared to infants born via cesarean section (61.1% vs 58.3%). The dominance of male infants in neonatal sepsis patients was also observed in nearly all prior studies from developing and developed countries (6,11). The imbalance of gender ratio in the incidence of neonatal sepsis and related mortality could be caused by factors such as genetic and chromosomal predisposition (17). Males are more susceptible to infection due to the presence of only one X chromosome, while females have two. The X chromosome contributes to the dimorphic nature of the inflammatory response during endotoxemia by diversifying the leukocyte response (18).

In this study, sepsis refers to both proven and unproven sepsis. This could impact some of the study's results, such as the fact that EOS was more common than LOS, contrary to several previous studies. A study in Australia conducted by Stoll et al. found that when not proven or clinical sepsis is examined, the prevalence of EOS (32%) is higher than LOS (26.6%). However, when only proven sepsis is considered, LOS (17.4%) is notably higher than EOS (1.3%) (19).

The most common birth route in neonatal sepsis patients was cesarean section (66.7%). However, statistical analysis showed no significant association between the birth route with neonatal sepsis in term infants ($p > 0.05$). A similar finding was also reported in a study conducted in Nepal (20). Term infants present a lower risk of neonatal sepsis than infants born preterm due to the presence of a mature immune system. IgG passively transports through the placenta from the mother to fetus in late pregnancy which begins at 13 weeks of gestation, while the largest amount is transferred at the last four weeks of pregnancy (21). The most common pathogen isolated from term neonatal sepsis patients is Group B streptococcus (GBS). A majority of them were born with GBS-colonized mothers who did not or inadequately received intrapartum antibiotic prophylaxis (22). A study by Yahya et al.

found that neonates born to GBS-colonized mothers who have an elective cesarean section after the commencement rupture of membranes or labor are more likely to be diagnosed with neonatal sepsis due to an unlikely obtainment of effective GBS chemoprophylaxis (23).

Birth route was found to correlate significantly with neonatal sepsis onset ($p < 0.05$). Infants born via cesarean section were found to be more at risk of developing EOS than vaginal delivery. A total of 76.5% EOS patients in this study was born via cesarean section. A study by Noah et a. et al. also found a high number of caesarean section of 85.28% in EOS patients. This high number might be associated to performed cesarean sections without medical indication, as a result of mothers desire for a rapid birth (24). EOS is caused by pathogen infections that are vertically transmitted from mother to child contracted through pregnancy or labour and manifest within the first three days of life (25).

Before birth, the fetus optimally is maintained in a sterile environment. In the intrapartum period, the mode of delivery may be a risk factor for neonatal sepsis. Organisms causing EOS ascend from the birth canal either when the amniotic membranes rupture or leak before or during the course of labor, resulting in intraamniotic infection. Neonates born with an instrumental delivery method are at risk for lacerations in approximately 0.1% to 3.1% of cesarean section deliveries. Laceration in neonates can be an entrance point for microorganisms, resulting in neonatal sepsis (26). A study by Adatara et al. found that infants who underwent an elective caesarean procedure were 83% less likely to have EOS than those who had an emergency caesarean section (27). There is little evidence comparing rates of suspected and confirmed neonatal sepsis in infants delivered through elective cesarean section vs planned vaginal birth. Hook et al. examined infection outcomes in 497 women undergoing elective repeated cesarean section compared to 492 women attempting vaginal delivery. In the elective repeat cesarean group, rates of both suspected and confirmed newborn sepsis were considerably lower (2% against 5%, p<

0.05) (28). Early detection of EOS is critical due to the significant burden of EOS despite the establishment of GBS screening in mothers and cautious antibiotic use (29).

A national cohort study by Olivier et al in Canada found that infants born via vaginal delivery or cesarean section had the same risk of developing LOS with OR = 0.99 (95% CI 0.87 – 1.12). However, the likelihood of LOS caused by coagulase-negative *Staphylococcal* neonatal sepsis (CONS)-associated infection was considerably greater among individuals who gave birth via cesarean section (10). Antibiotic exposure has the possibility of influencing the association between birth route with neonatal sepsis. In neonates delivered vaginally with perinatal antibiotic exposure, Tapiainen et al discovered a rapid alteration in the gut microbiota throughout the first week of life and transformation continuing up to 6 months (30). Intestinal bacteria play a vital role in developing the postnatal immune system, and a compromised immune system can make the infant more susceptible to infection (31).

A trend analysis of cesarean section rates of 121 countries between 1990–2014 found an increased rate of 12.4% with an annual average increase of 4.4% (32). Births by cesarean section necessitate a lengthier recovery time and result in a higher hospital stay duration than babies born via vaginal delivery (33). Prolonged duration of hospital stay has been identified as one of the factors associated with an increased risk of death in patients with neonatal sepsis (34). Bacterial contamination of instruments in the NICU is one of the sources of nosocomial infection. Poor hand hygiene and insufficient disinfection/fumigation are other factors that contribute. Adherence to strict infection control practices can prevent around one-third of nosocomial infections (35,36).

Conclusion

Delivery by cesarean section can increase the risk of early-onset sepsis in term infants. While a cesarean section can be life-saving, the procedure can also risk mothers and infants with long and short-term health problems if carried out without medical indication. Strict infection control protocols are needed in infants born by cesarean section who face a greater risk of nosocomial infection in EOS due to the requirement for invasive treatments.

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Tables

Table 1. Characteristics of the case and control study sample

Characteristics	Neonatal Sepsis	
	Yes	No
Birth weight (grams)		
Mean ± SD	2571.39 ± 625.837	2785.19 ± 658.606
Gestational age (weeks)		
Mean ± SD	38.33 ± 1.149	36.67 ± 2.548
Birth length (cm)		
Mean ± SD	43.24 ± 6.318	48.78 ± 3.045
Gender		
Male	32 (59.3%)	26 (48.1%)
Female	22 (40.7%)	28 (51.9%)
Total	54 (100%)	54 (100%)
Neonatal sepsis onset		
EOS	34 (63.0%)	-
LOS	20 (37.0%)	-
Total	54 (100%)	-
Mode of delivery		
Cesarean section	36 (66.7%)	31 (57.4%)
Spontaneous vaginal delivery	17 (31.5%)	20 (37.0%)
Forceps extraction	1 (1.8%)	3 (5.6%)

Total	54 (100%)	54 (100%)
Apgar score at 1st minute		
0– 6	27 (50.0%)	8 (14.8%)
7– 10	27 (50.0%)	46 (85.2%)
Total	54 (100%)	54 (100%)
Apgar score at 5th minute		
0– 6	18 (33.3%)	3 (5.6%)
7– 10	36 (66.7%)	51 (94.4%)
Total	54 (100%)	54 (100%)

Table 2. Association between mode of delivery with neonatal sepsis

Mode of delivery	Neonatal sepsis		p-value	Odds ratio (95% CI)
	Yes	No		
Cesarean section	36 (66.7%)	31 (57.4%)	0.321	1.48 (0.68 – 3.24)
Vaginal delivery	18 (33.3%)	23 (42.6%)		
Total	54 (100%)	54 (100%)		

Table 3. Association between mode of delivery with neonatal sepsis onset

Mode of delivery	Neonatal sepsis onset		p-value	Odds ratio (95% CI)
	EOS	LOS		
Cesarean section	26 (76.5%)	10 (50.0%)	0.046	3.25 (1.00 – 10.60)
Vaginal delivery	8 (23.5%)	10 (50.0%)		
Total	34 (100%)	20 (100%)		

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