

The Association between Birth Route and Early/Late-onset Neonatal Sepsis in Term Infants: A Case-control Study in the NICU of a Tertiary Hospital in East Java, Indonesia

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ABSTRACT

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

Methods: This hospital-based case-control study was carried out on term infants diagnosed with neonatal sepsis at the NICU of a tertiary referral hospital in East Java from 1 January 2019 to 31 December 2019. Preterm neonates were excluded as they may be more likely to develop neonatal sepsis. The Chi-square test and odds ratio (OR) with a confidence interval of 95% (CI=95%) were used to analyze data. P-value <0.05 was considered statistically significant.

Results: Of 54 patients with neonatal sepsis recruited, the majority had early-onset sepsis (63.0%) and cesarean section (C-section) delivery (66.7%). A significant association between birth route and neonatal sepsis onset ($p=0.046$) was found. However, no significant association was observed between birth route and neonatal sepsis ($p=0.321$). Term infants born via C-section were 3.25 times more at risk (95% CI 1.00 – 10.60) of early-onset neonatal sepsis than infants delivered vaginally.

Conclusion: C-section delivery can increase the risk of early-onset neonatal sepsis in term infants.

Keywords: Cesarean section, Neonatal sepsis, Term infants, Vaginal delivery.

Introduction

A key indicator of neonatal health and well-being is the neonatal mortality rate. This figure 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 were reported in the neonatal period. East Java is one of the provinces of Indonesia with the highest neonatal mortality rate. It accounted for around 80% of under-five mortality in 2017–2020. In 2020, the leading causes of neonatal death in Indonesia were low birthweight (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 reported between September–February 2015, sepsis was responsible for 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 challenge to neonatologists. Early-onset sepsis (EOS) and late-onset sepsis (LOS) are the

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two classifications of neonatal sepsis depending on the onset of symptoms (4). Potential maternal risk factors of neonatal sepsis include the 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 to alleviate 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 imposes a burden on the neonatal intensive care units (NICUs) due to the tendency to increase the survival rate of premature infants as a result of healthcare advancement in recent decades (9). There are still divergent results about the association between birth route and neonatal sepsis. Some studies have found a significant association between these two, while others have concluded otherwise (10–12). No study has investigated the association between birth route and neonatal sepsis onset in term infants. Thus, this study was conducted to identify the association between the birth route with EOS and LOS in term infants.

Methods

Study Design

This case-control study was carried out on neonates admitted to Dr. Soetomo Hospital, Surabaya, from 1 January 2019 to 31 December 2019. The total cases of neonatal sepsis in Dr. Soetomo Hospital Surabaya from 1 January 2019 to 31 December 2019 were 242. Of this figure, 161 patients were admitted to the NICU, among whom 107 out of 161 patients were born preterm. Therefore, after excluding premature neonates, 54 patients were recruited in the case group. The inclusion criteria consisted of 0–28 days of age, neonates admitted to the NICU of Dr. Soetomo General, term infants born after 37 full weeks of gestation, and infants diagnosed with neonatal sepsis based on clinical manifestations and laboratory tests assessed by physicians. Clinical features considered in this study were temperature instability (fever $\geq 38.0^{\circ}\text{C}$ and hypothermia $\leq 36.5^{\circ}\text{C}$), apnea, tachypnea, chest retraction, nasal flaring, tachycardia, cyanosis, hypotonia, hyporeflexia, and jaundice. The laboratory test components of a sepsis screen include a leucocyte count of $<5000/\text{cumm}$ or $>20.000/\text{cumm}$, an absolute neutrophil count $<2 \times 10^9/\text{L}$, I:T ratio of >0.2 and a C-Reactive Protein

(CRP) $>1\text{mg/L}$. Exclusion criteria were incomplete medical records of infants and/or laboratory results. Preterm neonates, defined as infants born before 37 full weeks of gestation, were excluded as they are more likely to develop neonatal sepsis. The 54 patients in the control group were selected by random sampling from among 1478 infants delivered in the obstetrics and gynecology emergency wards. Inclusion criteria for the control group were less than 28 days of age on admission, a final diagnosis other than neonatal sepsis, admission to the case group in the same year, and hospitalization in the same NICU as the comparison group.

Data collection

Secondary data was collected from the medical records of Dr. Soetomo Hospital. Based on the onset of symptoms, neonatal sepsis was categorized into early-onset sepsis (EOS) if appearing less than 72 hours following birth and late-onset sepsis (LOS) if presenting after 72 hours. Mode of delivery was classified based on the birth canal route, i.e., C-section and vaginal delivery.

Ethical issues

The study was approved by the ethics committee of Dr. Soetomo Hospital, Surabaya, Indonesia (No. 0371/105/XI/2020). The patients were assured about the confidentiality of the medical records gathered during the study.

Statistical analysis

The bivariate analysis was conducted using the Chi-square test. P-value < 0.05 was considered statistically significant. For the univariate analysis of continuous data, mean \pm SD was used and for categorical data, frequency and percentages were utilized. The odds ratio (OR) with 95% CI was used to estimate the strength of the correlation. All tests were carried out using SPSS ver. 25.0.

Results

Table 1 outlines the mean birthweight of both cases (2571.39 ± 625.837 g) and the control group (2785.19 ± 658.606 g). Both groups had a normal birthweight of above 2500 g. The mean gestational age of the study group (38.33 ± 1.149 weeks) was higher than the control group (36.67 ± 2.548 weeks). The birth length of infants was shorter in the study group (43.24 ± 6.318 cm)

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 1 st 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 5 th 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 the mode of delivery and 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%)		

than in the control group (48.78 ± 3.045 cm). The majority of patients were male in the study group (59.3%). Also, female neonates (51.9%) outnumbered male ones (48.1%) in the control group. C-section was the dominant delivery mode of infants in the study group (66.7%) and the control (57.4%). The neonatal sepsis onset relative to all subject characteristics was EOS 63% and LOS 37%.

Most neonates had a 5-min Apgar score of 7-10, (Case group: 66.7%, Control: 94.4%).

The results of the bivariate analysis by Chi-square test with a p-value > 0.05 (p = 0.321) did not show any significant associations between birth route and neonatal sepsis (Table 2). However, as shown in Table 3, there was a significant association between birth route and neonatal sepsis onset in term infants (p = 0.046). Term infants born by C-section were 3.25 times more at the risk (95% CI 1.00 - 10.60) of early-onset neonatal sepsis than vaginal delivery.

Table 3. Association between the mode of delivery and the 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%)		

Discussion

Neonates are subject to immunological immaturity that provokes susceptibility to infection. Understanding the risk factors helps predict critical illnesses, such as sepsis at its early stages (13). The risk factors of neonatal

sepsis in the perinatal period cannot be controlled and the direct diagnosis is challenging, which explains the high morbidity and mortality rate (14). Low birth weight (LBW) has been a strong risk factor for neonatal sepsis (15). The immaturity of the body organs and

difficulty to feed and digest breast milk in LBW infants interfere with the development of the immune system, increasing neonatal predisposition to infection (16). The mean birthweight of neonatal sepsis in this study was normal, contrary to the results reported in the literature. Premature infants and the majority of low birthweight infants were excluded from the study.

This study found the highest incidence of neonatal sepsis in male infants (56.2%). The incidence of neonatal sepsis in infants born by vaginal delivery was higher in male subjects, but it was not significantly different from infants born by C-section (61.1% vs 58.3%). A greater number of male infants with neonatal sepsis was also reported in the research conducted in developing and developed countries (6,11). The gender imbalance in the incidence of neonatal sepsis and related mortality could be attributed to factors such as genetic and chromosomal predisposition (17). Males are more susceptible to infection due to the presence of only one X chromosome. The X chromosome is responsible for the dimorphic nature of the inflammatory response during endotoxemia by diversifying the leukocyte response (18).

In this study, we used the term sepsis to describe both proven and unproven cases of sepsis. This may impact some of the results, including the fact that EOS was more common than LOS, as opposed to the results reported in many previous studies. A study by Stoll et al. in Australia found that unless proven or clinical sepsis is accounted for, the prevalence of EOS (32%) will be higher than LOS (26.6%). However, when only proven sepsis is considered, LOS (17.4%) will be considerably higher than EOS (1.3%) (19).

The most common birth route in neonatal sepsis patients was C-section (66.7%). However, statistical analysis did not reveal a significant association between the birth route and neonatal sepsis in term infants ($p > 0.05$). A similar finding was also reported by Nepal (20). Term infants are at a lower risk of neonatal sepsis than preterm infants due to their immature immune systems. IgG is passively transferred through the placenta from the mother to the fetus in late pregnancy which begins at 13 weeks of gestation. However, the largest portion is transferred in 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 infants were born to GBS-colonized

mothers who either did not receive or inadequately received intrapartum antibiotic prophylaxis (22). A study by Yahya et al. found that neonates born to GBS-colonized mothers who had an elective C-section after the rupture of membranes or labor are more likely to be diagnosed with neonatal sepsis due to an impossibility of obtaining an effective GBS chemoprophylaxis (23).

The birth route was found to be significantly correlated with the onset of neonatal sepsis ($p < 0.05$). Infants born by C-section were at a greater risk of developing EOS than those born by vaginal delivery. A total of 76.5% of EOS patients in this study were born by C-section. Noah et al. also reported a higher prevalence of C-sections in EOS patients (85.28%). This might be due to C-sections performed without medical indication, driven by the mother's desire for a rapid birth (24). EOS is caused by pathogen infections that are vertically transmitted from mother to child through pregnancy or labor and manifest within the first three days of life (25).

Before birth, the fetus is optimally maintained in a sterile environment. In the intrapartum period, the delivery mode 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 labor, leading to the intraamniotic infection. Neonates born by instrumental delivery are at the risk of lacerations in approximately 0.1% to 3.1% of C-section deliveries. Laceration in neonates can be a window for the transmission of microorganisms that cause neonatal sepsis (26). A study by Adatara et al. found that infants undergoing an elective cesarean procedure were 83% less likely to develop EOS than those who had an emergency C-section (27). There is a paucity of evidence on comparing the suspected and confirmed neonatal sepsis in infants delivered by elective C-section vs planned vaginal delivery. Hook et al. explored infection outcomes in 497 women undergoing elective repeated C-sections as opposed to 492 women undergoing vaginal delivery. In the former group, the rates of both suspected and confirmed cases of newborn sepsis were considerably lower (2% vs. 5%, $p < 0.05$) (28). The 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 by vaginal delivery or C-section ran the same risk of developing LOS

with OR=0.99 (CI =95% 0.87 – 1.12). However, the likelihood of LOS caused by infection due to the coagulase-negative *Staphylococcal* (CONS) was considerably greater in individuals who had C-section delivery (10). Antibiotic exposure can affect the association between birth routes and neonatal sepsis. In their study on neonates delivered vaginally with perinatal antibiotic exposure, Tapiainen et al. discovered a rapid alteration in the gut microbiota within the first week of life and transformation 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 C-sections in 121 countries between 1990–2014 found an increased rate of 12.4% with an annual average increase of 4.4% (32). C-section delivery prolongs the recovery time and increases the higher hospital stay compared to infants born by vaginal delivery (33). Prolonged hospital stay has been identified as one of the factors associated with the increased risk of mortality 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 contributing factors. Adherence to strict infection control practices can prevent around one-third of nosocomial infections (35,36).

Conclusion

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

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Conflicts of interest

The authors have no conflict of interest regarding the publication of this study

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