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Original Article

The association between premature rupture of membranes (PROM) and preterm gestational age with neonatal sepsis: a systematic review and meta-analysis

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Abstract

Background Sepsis is one of the main causes of neonatal mortality. The morbidity and mortality rates due to neonatal sepsis are as high as 9-20%. Premature rupture of membranes (PROM) and preterm gestational age are among the risk factors of neonatal sepsis.

Objective To evaluate for potential associations between PROM as well as preterm gestational age to neonatal sepsis by meta-analysis and systematic review.

Methods A meta-analysis and systematic review were performed using literature sourced from *PubMed, Cochrane,* and *Google Scholar* according to PRISMA guidelines. We calculated the incidence of sepsis in neonates with and without PROM and premature gestational age. Journal quality was assessed according to the *Newcastle-Ottawa Scale* (NOS) criteria.

Results From the literature search for PROM, 21 case-control studies met the inclusion criteria. Neonatal sepsis was more common in neonates who had a maternal history of PROM than in those without [OR 2.69 (95%CI 1.56 to 4.65); P<0.00001]. From the literature search for gestational age, we found 17 case-control studies that met the inclusion criteria. Neonatal sepsis was more common in preterm than term neonates [OR 2.55 (95%CI 1.61 to 4.04); P<0.00001].

Conclusion Neonates with a maternal history of PROM and/or preterm gestational age are at high risk of developing neonatal sepsis. **[Paediatr Indones. 2023;63:152-61; DOI: https://doi.org/10.14238/pi63.3.2023.152-61**].

Keywords: *neonatal sepsis; infection; premature rupture of membranes; PROM; gestational age; preterm*

The first 28 days of life, also known as the neonatal period, are crucial for a child's growth and development.[1] However, this period also has the highest risk of death across childhood. In 2019, the neonatal mortality rate was 17/1,000 live births globally.[2] The most frequent causes of deaths in neonates are complications of prematurity (35%), intrapartum complications (24%), sepsis (15%), congenital abnormalities (11%), pneumonia (6%), tetanus (1%), and diarrhea (1%).[3,4]

Systemic multi-organ dysfunction triggered by systemic microorganism infection is known as sepsis. Diagnosing neonatal sepsis is challenging for clinical practitioners because of its nonspecific clinical signs that often overlap with those of other diseases.[5] Neonatal sepsis is one of the critical health care priorities of the *World Health Organization* (WHO) due to its high morbidity and mortality rates despite progress in diagnosis and treatment.[6]

Some conditions, such as prematurity, low birth weight, premature rupture of membranes (PROM),

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non-spontaneous labor (especially cesarean section), and lack of postpartum care are known to raise the incidence of neonatal sepsis.[7] A previous meta-analysis reported that four out of ten neonates who developed sepsis tended to have fatal morbidities, and premature neonates had the worst results.[8] Premature rupture of membrane (PROM) is associated with ten times increased risk of neonatal sepsis, while preterm gestational age increases the risk of sepsis by three to ten times.[9] A study in Banjarmasin also showed that prolonged labor, PROM, and preterm gestational age were significant risk factors of neonatal sepsis, with the latter two being the most influential.[10] The risks are compounded when PROM and prematurity coexist, termed preterm premature rupture of membrane (PPROM). Although mortality rates due to neonatal sepsis have decreased, long-term consequences are a major concern, especially for brain and nervous system development.[11,12] In order to prevent neonatal sepsis, many countries have improved health services quality and access for mothers during pregnancy and childbirth. Although preventive services are sometimes constrained by a lack of financial and human resource factors in middle- to low-income countries, there are a number of easy and low-cost but promising interventions, including education and control of risk factors.[13]

The purpose of this meta-analysis was to further evaluate the degree of influence of PROM and preterm gestational age on neonatal sepsis. We hope that the results of our meta-analysis and systematic review can inform future guidelines for the effective prevention of neonatal sepsis.

Methods

We searched the online literature databases *PubMed, Cochrane*, and *Google Scholar*. As keywords, we used the MeSH terms "neonatal sepsis" OR "neonatal infection" OR "sepsis" AND "premature rupture of membranes" OR "PROM" OR "PPROM" and "neonatal sepsis" OR "neonatal infection" OR "sepsis" AND "gestational age" OR "premature" OR "postterm". The literature search process was carried out from June 10 to October 15, 2021.

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) statement.[14] The articles met the established inclusion criteria outlined in **Table 1**.

Research articles with unsuitable titles, duplicates, articles that were not available in full-text, studies with different objectives, no control group, or unsuitable study design, articles in languages other than English or Indonesian, and articles that did not meet the quality criteria were excluded.

Neonatal sepsis was defined as a systemic bacterial, viral, or fungal infection occurring in neonates (<28 days of age) which causes hemodynamic changes and other clinical manifestations, thereby increasing morbidity and mortality in neonates. A diagnosis of neonatal sepsis can be made if there are at least two clinical manifestations and two laboratory parameters typical of sepsis, in accordance with the *European Medicines Agency* (EMA) *Sepsis Scoring System*.[15] Premature rupture of membranes (PROM) was defined as the rupture of the amniotic membrane before the delivery process, which can occur at preterm or full-term gestation. Gestational age was defined as time from conception as the beginning of pregnancy until delivery and was classified as preterm (<38 weeks), full-term (38 to 42 weeks), and post-term (>42 weeks).

Two reviewers collected articles according to previously set data collection standards with regards to characteristics, comparisons, and outcomes. All articles were screened and selected according to the

Table 1. Article inclusion criteria

Variables	Remarks
Patients	Neonates aged 0-28 days who have been diagnosed with sepsis and a non-sepsis control group
Intervention/predictors	Maternal risk factors for PROM or abnormal gestational age (premature or post-term)
Comparison	Absence of maternal risk factors for PROM or full-term gestational age
Outcome	The incidence of neonatal sepsis
Study design and period	Case-control studies published in 2016 to 2021

inclusion criteria. To assess the risk of bias, we used the *Newcastle-Ottawa Scale* (NOS).[16] All included studies had an adequate sample size and statistically accurate hypothesis tests. Studies were rated based on risk of bias; the highest possible rating of nine stars corresponded to the lowest risk of bias, consisting of a maximum of four stars for the selection category, two stars for the comparability category, and three stars for the exposure category. To be included in the meta-analysis, research articles must have had a minimum score of "adequate."

This meta-analysis was conducted using *Review Manager 5.4* software (*The Cochrane Collaboration*, Oxford, UK). We computed odds ratios (ORs) with 95% confidence intervals (95%CI) for each variable. A P value of <0.05 was considered statistically significant. The Cochran Q test was used to assess the heterogeneity (I^2) of the data. We used a fixed-effects model if the I2 value was less than 50% and a random effects model if I2 was more than 50%. The overall research hypothesis was measured by the Z-test.

Results

The literature search yielded 7,056 PROM research articles, of which 21 were included in the meta-analysis and systematic review (**Figure 1**). The characteristics of included studies are shown in **Table 2**. Most of the 21 PROM articles came from Asian countries [Israel (1), India (3), Turkey (2), Iraq (1), Korea (1), Iran (2), Papua New Guinea (1), Sri Lanka (1), China (1), Nepal (1)]; three African countries: Ghana (1), Ethiopia (3), and Tanzania (1), Australia

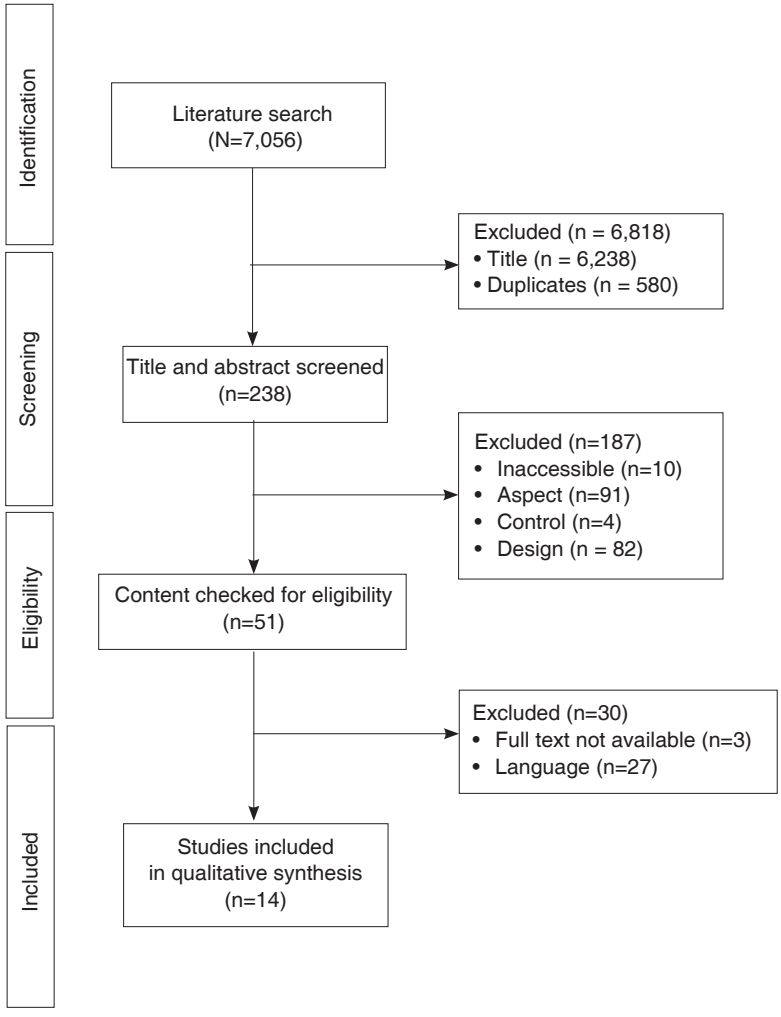

Figure 1. Literature search for PROM according to PRISMA

(1), and USA (1)]. Fourteen articles were on PROM and 7 were on PPROM. All 21 articles met the quality criteria for further analysis based on their NOS score.

Results of our meta-analysis of the 21 studies evaluating the influence of PROM on the occurrence of neonatal sepsis are presented in **Figure 2**. Only two studies found the incidence of PROM to be smaller in the non-sepsis than the sepsis group.7,24 Eleven studies found a higher incidence of PROM in the sepsis than the non-sepsis group.[17,18,23,26,27,29,31,33,37-39] In the remaining eight studies, the ORs were not statistically significant.[19-22,25,28,30,35] Since the data were heterogenous (I^2=86%), a random effects model was used for analysis. We obtained a pooled OR of 2.69 (95%CI.56 to 4.65; P< 0.00001).

Regarding gestational age, the literature search yielded 5,591 studies, 17 of which were included in the meta-analysis (**Figure 3**). The characteristics of the included studies are shown in **Table 3**. Most studies came from Asian countries [Indonesia (1), India (1), Iraq (1), Korea (1), Iran (2), and Nepal (1)], followed by three African countries: Ethiopia (4), Ghana (1), Tanzania (1), two North American countries: Mexico (1) and USA (2), and Australia (1)]. All included studies evaluated prematurity. All 17 articles met the quality criteria for further analysis based on their NOS score.

Results of our meta-analysis of the 17 studies evaluating the influence of prematurity on the occurrence of neonatal sepsis are presented in **Figure 4**. Only one study found the incidence of prematurity to be smaller in the non-sepsis than the sepsis group.35 In ten studies, the incidence of prematurity was higher in the sepsis than the non-sepsis gro up.[7,9,17,18,22,24,27,29,36,39] The remaining six studies found statistically non-significant ORs.[19,20,28,30,33,34] Since the data were heterogenous (I^2=86%), a random effects model was used for analysis. The pooled OR was 2.55 (95%CI 1.61 to 4.04; P<0.00001).

Table 2. Study characteristics of PROM

Research article, year of publication	Location	NOS score	Case setting	PROM in sepsis patients (%)	PROM in control patients (%)	OR
Adatara *et al.*[7], 2019	Ghana	7	PROM	3/103 (2.9)	116/797 (14.5)	0.18
Alemu *et al.*[27], 2019	Ethiopia	7	PROM	29/82 (35.3)	14/164 (8.5)	5.86
Bauer *et al.*[17], 2019	America and Israel	8	PROM	10/82 (12.1)	6/328 (1.8)	7.45
Bhargava *et al.*[35], 2017	India	8	PROM	7/24 (29.1)	3/26 (11.5)	3.16
Braye *et al.*[18], 2019	Australia	6	PROM	34/65 (52.3)	8847/91990 (9.6)	10.31
Dundar *et al.*[25], 2018	Turkey	6	PPROM	19/28 (67.8)	31/72 (43.0)	2.79
Gebremedhin *et al.*[33], 2016	Ethiopia	6	PROM	24/78 (30.7)	6/156 (3.8)	11.11
Jameel *et al.*[29], 2020	Iraq	7	PROM	28/100 (28.0)	3/100 (3.0)	12.57
Masanja *et al.*[38], 2020	Tanzania	7	PPROM	15/105 (14.2)	14/217 (6.4)	2.42
Mishra *et al.*[39], 2021	India	7	PPROM	21/30 (70.0)	29/70 (41.4)	3.30
Moon *et al.*[30], 2021	Korea	7	PPROM	16/33 (48.4)	134/255 (52.5)	0.85
Naseh *et al.*[19], 2021	Iran	6	PROM	3/20 (15.0)	0/34 (0)	13.8
Nikpay *et al.*[20], 2019	Iran	6	PROM	2/15 (13.3)	29/129 (22.4)	0.53
Olita'a *et al.*[21], 2019	Papua New Guinea	8	PROM	7/10 (70.0)	98/123 (79.6)	0.60
Ozel *et al.*[26], 2020	Turkey	7	PPROM	31/31 (100.0)	29/76 (38.1)	101.44
Palatnik *et al.*[22], 2019	America	7	PPROM	31/73 (42.4)	276/706 (39.0)	1.15
Perera *et al.*[37], 2018	Sri Lanka	7	PROM	25/161 (15.5)	0/120 (0)	45.02
Sharma *et al.*[23], 2016	India	6	PPROM	6/17 (35.2)	0/21 (0)	24.30
Sorsa *et al.*[28], 2019	Ethiopia	7	PROM	33/88 (37.5)	59/215 (27.4)	1.59
Wen *et al.*[31], 2021	China	6	PROM	49/90 (54.4)	53/151 (35.0)	2.21
Yadav *et al.*[24], 2021	Nepal	7	PROM	2/59 (3.3)	77/291 (26.4)	0.10

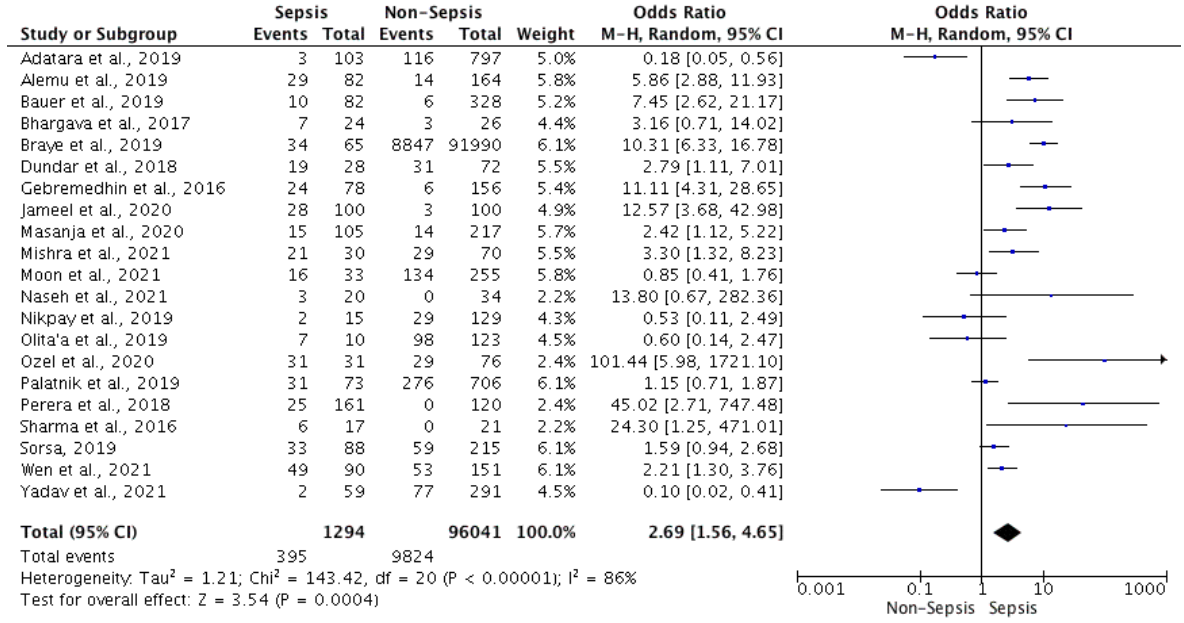

Figure 2. Forest plot of PROM incidence among sepsis and non-sepsis groups

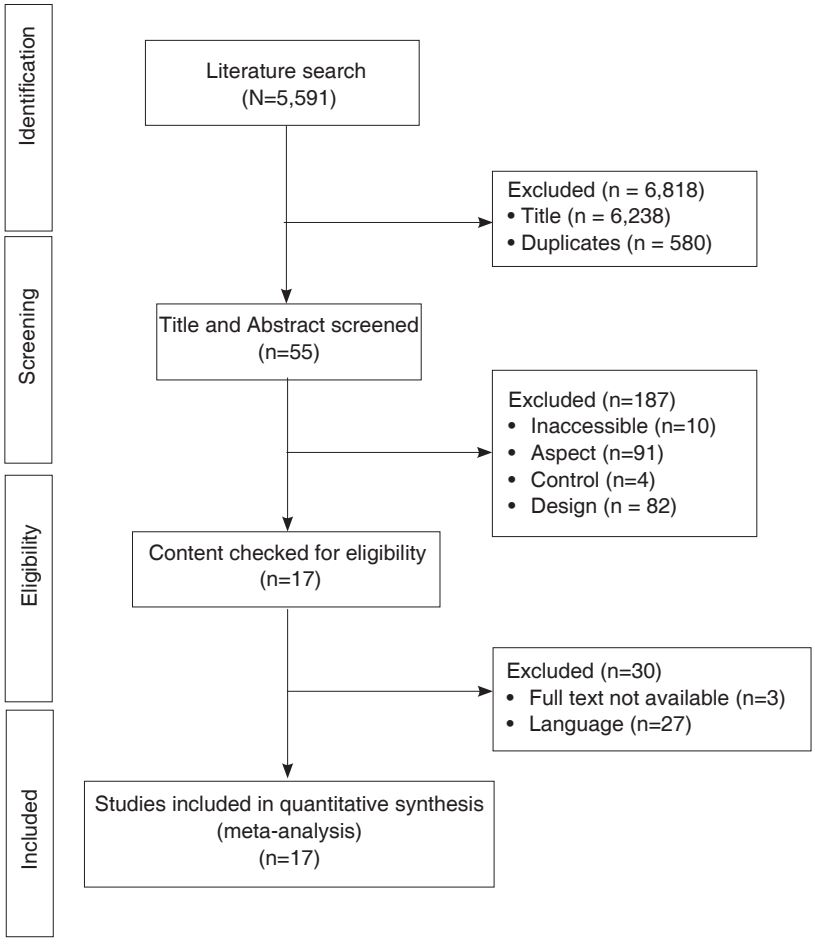

Figure 3. Literature search for gestational age according to PRISMA

Table 3. Study characteristics of gestational age

Research article, year of publication	Location	NOS score	Premature in sepsis patients (%)	Premature in control patients (%)	OR
Adatara *et al.*[7], 2019	Ghana	7	25/103 (24.2)	77/797 (9.6)	3.00
Alemu *et al.*[27], 2019	Ethiopia	7	50/82 (60.9)	40/164 (24.3)	4.84
Balderrama *et al.*[34], 2016	Mexico	7	35/43 (81.3)	33/42 (78.5)	1.19
Bauer *et al.*[17], 2019	America and Israel	8	16/82 (19.5)	16/328 (4.8)	4.73
Bhargava *et al.*[35], 2017	India	8	5/24 (20.8)	13/26 (50.0)	0.26
Braye *et al.*[18], 2019	Australia	6	43/65 (66.1)	8122/91990 (8.8)	20.18
Bulto *et al.*[36], 2021	Ethiopia	7	72/188 (38.2)	61/356 (17.1)	3.00
Gebremedhin *et al.*[33], 2016	Ethiopia	6	22/78 (28.2)	27/156 (17.3)	1.88
Jameel *et al.*[29], 2020	Iraq	7	31/100 (31.0)	12/100 (12.0)	3.29
Masanja *et al.*[38], 2020	Tanzania	7	13/105 (12.3)	11/217 (5.0)	2.65
Moon *et al.*[30], 2021	Korea	7	17/33 (51.5)	121/255 (47.4)	1.18
Naseh *et al.*[19], 2021	Iran	6	2/20 (10.0)	6/34 (17.6)	0.52
Nikpay *et al.*[20], 2019	Iran	6	7/15 (46.6)	65/129 (50.3)	0.86
Ocviyanti *et al.*[9], 2018	Indonesia	6	20/21 (95.2)	199/384 (51.8)	18.59
Palatnik *et al.*[22], 2019	America	7	48/73 (65.7)	162/706 (22.9)	6.45
Sorsa *et al.*[28], 2019	Ethiopia	7	20/88 (22.7)	49/215 (22.7)	1.00
Yadav *et al.*[24], 2021	Nepal	7	22/59 (37.2)	48/291 (16.4)	3.01

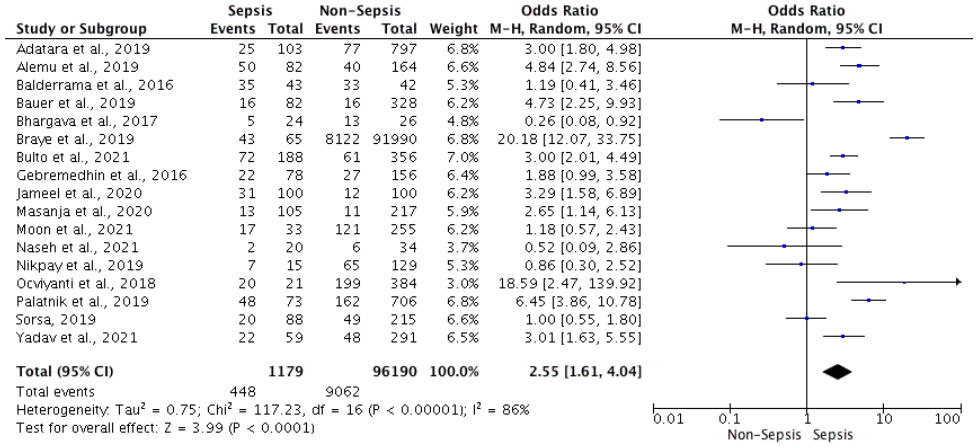

Figure 4. Forest plot of gestational age (premature) incidence among sepsis and non-sepsis groups

Discussion

Our meta-analysis of 21 studies revealed PROM as a significant risk factor for neonatal sepsis. The results of this meta-analysis are in line with the results of most of the studies included in the meta-analysis.[7,17-24] The association between PROM and neonatal sepsis may be influenced by the longer time interval between rupture of the membranes and delivery, which may lead to further complications. Dundar *et al.*[25] reported on such complications, including respiratory distress syndrome (RDS), intraventricular hemorrhage, necrotizing enterocolitis, and neonatal sepsis. The same study also reported that sepsis was one of the most frequent complications in neonates whose mothers had a history of PPROM (P=0.02). Furthermore, Ozel *et al.*[26] reported that neonatal sepsis was the most common complication in infants with

a history of PPROM, along with incidence of NICU admission. Infection or inflammation initiated by platelet activation is believed to be a fairly important actor that can initiate the occurrence of PROM.

Alemu *et al.*[27] also reported that PROM is a significant risk factor for the incidence of neonatal sepsis, especially if PROM occurs more than 18 hours prior to delivery, with an adjusted OR for neonatal sepsis of of 2.81 (95%CI 1.01 to 7.79). Another study reported that neonates whose mothers had PROM had an OR of 2.31 for developing sepsis (95%CI 0.94 to 5.65) due to ascending colonization of microorganisms from the birth canal.[28] Similarly, Jameel *et al.*[29] noted that PROM increased the opportunity for microorganisms to ascend from the birth canal to the amniotic sac, potentially leading to sepsis. Chorioamnionitis can induce asphyxia, which in turn can facilitate infection in the uterus. Leukocyte activity it requires energy (ATP) for cytoskeletal microfilament contractions, therefore inhibited by hypoxia. A hypoxic state will also inhibit the microbicidal activity of polymorphonuclear cells. Cervical incompetence, umbilical cord prolapse, and malpresentation associated with prematurity can also cause PROM and lead to neonatal sepsis.[27]

Moon *et al.*[30] further investigated the association between intra-amniotic inflammatory response and the development of inflammation in the extraplacental membrane as well as the anatomic relationship between the extraplacental membrane and the chorionic plate that causes inflammation to continue to develop. This condition can increase the likelihood of developing sepsis in neonates. They also further divided the development of inflammation in the chorionic plate into three stages. Mothers with a history of PPROM had a 1.773 times higher risk for stage-1 inflammation (inflammation limited to subchorionic fibrin), a 1.097 times higher risk for stage-2 inflammation (inflammation that spreads to the connective tissue), and 0.423 times the risk for stage-3 inflammation (chorionic vasculitis). Although the risk for stage-3 inflammation was reduced, infants from mothers with a history of PROM are at a heightened risk of neonatal sepsis.

Wen *et al.*[31] also noted that maternal history of PROM was more common in neonates with sepsis because the need for induced labor increases after PROM, leading to an increase in the frequency of vaginal examinations and further disrupting the balance of normal vaginal flora, weakening the immune system, and increasing the opportunity for pathogenic microorganisms to enter the vagina, blood, uterine cavity, and abdominal cavity through wounds in the reproductive tract and leads to sepsis.

Overall, both term and preterm PROM were associated with neonatal sepsis. Our results were in agreement with a previous meta-analysis by Abate *t al.*[32] who also found a significant relationship between PROM and neonatal sepsis (aOR=1.95; 95%CI 0.53 to 3.37; I2=43.2%; P=0.062).

Our meta-analysis of 17 studies on gestational age as a risk factor for neonatal sepsis showed that preterm gestational age was indeed associated with the incidence of neonatal sepsis. The results of our meta-analysis are in line with the results of several of the included previous studies. [7,9,17,18,22,24,27,29,36,38] Another prior study found that prematurity was the most common risk factor for neonatal sepsis. The immune system is not fully developed in premature infants, creating a good environment for microorganisms to move and multiply, potentially leading to sepsis. In addition, premature neonates are often admitted to the NICU and hospitalized for a longer duration than full-term infants, increasing the risk of a hospital-acquired infection.[20]

Moon *et al.*[30] more specifically reported that premature birth was a risk factor for early-onset neonatal sepsis (EONS). Early-onset neonatal sepsis is associated with one of the causes of preterm birth, namely, ascending infection originating from the vaginal-cervical canal through the choriodecidua to the chorionic blood vessels or amniotic cavity, eventually invading the fetus. Ascending intrauterine infection also causes an inflammatory response in every part of the placental compartment such as the extraplacental membrane, chorionic plate, umbilical cord, and amniotic fluid. During the development of ascending intrauterine infection in the extraplacental membrane, maternal neutrophils migrate from the parietal decidua through the trophoblast membrane and chorionic connective tissue to the amnion. The development of this inflammatory process within the extraplacental membrane is associated with an increased progression of infection to sepsis.[30]

Braye *et al.*[18] also found that the incidence of EONS was highest in the premature infant group,

with two-third of the total incidence of neonatal sepsis occurring in this group. Although there has been a decrease in the incidence of EONS in premature infants due to improved management (timely and well-targeted diagnosis and treatment), the majority of EONS still occurs in premature infants. This finding could be due to the fact that most premature babies do not benefit from antenatal care screening in the third trimester and the lack of group-B Streptococcus (GBS) vaccination for pregnant women. If the mother and fetus are thoroughly examined at term pregnancy, even if infection occurs, it can be treated quickly and appropriately so that it does not lead to sepsis.

Balderrama *et al*.[34] noted that prematurity was the second most common risk factor of neonatal sepsis (OR=10.8) after maternal infection, especially at <28 weeks' gestational age. This was associated with the incidence of chorioamnionitis, which is more common in premature infants. Chorioamnionitis (CAM) is inflammation of the chorioamniotic membrane that occurs in 2-4% of term births and 40-70% of preterm births. Chorioamnionitis is characterized by symptoms such as fever, abdominal pain, abnormal vaginal discharge, and leukocytosis, as well as the histology of inflammation and necrosis throughout the chorionic plate and amnion. The more premature a baby is, the higher the likelihood of developing chorioamnionitis. The previous study noted that 67% of infants born at 21-24 weeks' gestation had a history of maternal chorioamnionitis, which was much higher than a history of maternal chorioamnionitis in infants born at 33-36 weeks, which was 22%.[34] Chorioamnionitis was associated with high maternal and neonatal morbidity and mortality, including an increased risk for neonatal sepsis, pneumonia, intraventricular hemorrhage, neurological damage, cerebral palsy, periventricular leukomalacia, and chronic lung disease.[34]

The immunity of infants who are still very immature at birth is also a risk factor strongly associated with the incidence of neonatal sepsis. This risk will continue to increase as gestational age decreases, this was stated by Bhargava *et al*.[35] The study added that physiologically, antibodies from the mother in the form of IgG will be transferred to the fetus through the placenta. This process does not take place or takes place imperfectly in premature babies. Not only that, premature babies also usually require invasive procedures such as umbilical catheterization or intubation. This study is supported by Bulto *et al*.[36] Alemu *et al*.[27] also noted that preterm birth was a risk factors for neonatal sepsis, with 6.9 times higher risk than full term birth. Premature neonates have weak immune systems that are prone to infection and may lead to sepsis. Furthermore, premature neonates are also more likely to receive additional supportive care such as intravenous parenteral nutrition or insertion of a respirator, thereby increasing the neonate's exposure to infectious microbes. In addition, premature infants have immature skin and mucosal barriers that further exacerbate their predisposition to infection and sepsis if they need prolonged intravenous access. Premature infants also have low blood volume and often receive early antimicrobial therapy which can create false-negative culture results. This complicates diagnosis and delays the management of neonatal sepsis.

Some studies included in our meta-analysis on gestational age and neonatal sepsis, did not show significant differences between premature and term infants in the incidence of neonatal sepsis.[19,20,28,30,33,34] Differences in the selection of control groups or in the diagnosis of sepsis may have led to this result. Sorsa[28] reported a 39% prevalence of neonatal sepsis, which was lower than reports submitted from other countries (45.9%) because other countries used much stricter criteria to define neonatal sepsis.

In conclusion, neonates with a history of PROM or preterm birth have an increased risk for developing neonatal sepsis. Clinicians should take these risks into consideration, so that proper management can be done earlier to prevent the occurrence of fatal neonatal sepsis.

Conflict of interest

None declared.

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