Medical Science

Neonatal sepsis in association with birth weight, gestational age, and mode of delivery in Saudi Arabia: A systematic review and meta-analysis

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ABSTRACT

Introduction: Neonatal sepsis is a worldwide health problem. Additionally,
neonatal sepsis causes a great burden of morbidity and mortality in
developing countries. *Methodology*: A systematic search in PubMed, Web of
Science, Science Direct, and EBSCO databases, was conducted. The reviewers
screened the extracted literature to include the studies that met the inclusion
criteria. *Results:* A total of 119 articles were reviewed, of which 4 study articles
were included in this meta-analysis. We found that birth weight was not
significantly related to the risk of neonatal sepsis (n=4; SMD -0.68; 95% CI [-
0.89, -0.46]). Gestational age did not have a significant effect on the rate of
occurrence of neonatal sepsis (n=3; SMD -0.17; 95% CI [-0.41, -0.06]). Vaginal
delivery mode is associated with lower incidence of neonatal sepsis (n=3; OR
0.61; 95% CI [0.36, 1.03]). The cesarean section was associated with a higher
incidence of neonatal sepsis (n=3; OR 2.13; 95% CI [1.23, 3.70]). *Conclusion*: This
study found that both neonatal and maternal factors as potential independent
risk factors to have an association with the risk of neonatal sepsis. We also
observed that birth weight, gestational, and vaginal deliveries are not
associated with a higher risk of neonatal sepsis, while cesarean delivery was
associated with greater risk.

Keywords: Neonatal Sepsis, Birth Weight, Gestational Age, Mode of Delivery,
Saudi Arabia, Meta-analysis

DISCOVERY
SCIENTIFIC SOCIETY

1. INTRODUCTION

A recent report by the WHO has presented sepsis as a critical healthcare
priority for the coming decades. Sepsis is life-threatening bloodstream
infection (Hotchkiss et al., 2016). Ranking incidence and mortality rates of
sepsis occur in extreme age groups, with young children, newborn babies, and
elderly at greatest risk (Singer et al., 2016). Neonatal sepsis conditions are

categorized to early onset of sepsis (EOS) and late-onset sepsis (LOS). Regarding the early onset of neonatal sepsis, 85% occur within 24 h, 5% occur within 24-48 h, and smaller percentages occur within 48-72 h (Bulkowstein et al., 2016). EOS was associated with microorganisms' acquisition from the mother, birth canal within during (Bulkowstein et al., 2016).

Globally, the number of newborn deaths dropped from 5 million in 1999 to 2.5 million in 2017. More than 40% of all deaths of children under the age of five happened during the neonatal era (WHO, 2018). The WHO reports that neonatal sepsis causes 1 million deaths per year (10% of all deaths in children under the age of five), with 42% of these deaths happening one week after birth. Preterm delivery (28%), serious infections (26%), and asphyxia are considered to be the top direct causes of neonatal death worldwide (23%), (Lawn et al., 2005).

EOS means that, the blood and/or cerebrospinal fluid culture-positive infection that occurs within three days after birth, typically caused by maternal vertically transmitted organisms to the neonate. Furthermore, LOS arises after of birth by about three days, and it is usually caused by pathogens infection during the hospital care course (Stoll et al., 2002). The neonatal sepsis incidence varies from 10-50/1000 live birth in developing countries and 10-50/1000 live birth in developing countries (McIntosh et al., 2003). There are numerous risk factors for developing neonatal sepsis, such as low birth weight, prolonged rupture of membranes over 24 hours, unsafe place of delivery or non-sterilized delivery, chorio-aminonitis, perinatal asphyxia, maternal pyrexia, and prolonged labor (Bennet et al., 1985).

It has been reported recently that low birth weight and reduced gestational age lead to the hazard of occurrence of fatal cardiovascular changes among adults born prematurely (Mercuro et al., 2013). Regarding the causative organism, gram-positive bacteria were found to be the most prevalent isolated organisms in LOS (Joseph et al., 2012). At the same time, gram-negative pathogens were more common among underweight infants at birth with EOS (Hornik et al., 2012). Adatara et al., (2018) reported that cesarean section delivery was significantly related to the risk of occurrence of neonatal sepsis (Adatara et al., 2018). Although newborns delivered via cesarean section overcome the vaginal bacteria, they frequently have a prolonged hospital stay and a delayed start to breastfeeding (Mueller et al., 2015). Delayed breastfeeding in CS deliveries can deprive the neonate of colostrum's protective effect against various pathogenic microbes that are harmful to the newborn (Yu et al., 2018).

This study aims to determine the association amongst birth weight, gestational age, type of delivery, and risk of neonatal sepsis in Saudi Arabia.

2. METHODOLOGY

Study design
A systematic review and meta-analysis directed conferring to the Meta-analysis of descriptive Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000).

Study duration
From March 1, 2021 to March 15, 2021

Study conditions
Neonatal sepsis

Population and Control
Neonates with sepsis have been investigated for the presence of blood stream or cerebrospinal fluid infection. The control group included healthy newborns with no history of sepsis.

Search strategy
A systematic exploration was in PubMed, Web of Science, Science Direct and EBSCO databases using boolean operators AND, and OR as follows: ((Neonatal sepsis) AND (gestational age)) AND (Saudi Arabia), (("Neonatal Sepsis"[Mesh]) AND "Birth Weight"[Mesh]) AND "Saudi Arabia"[Mesh],((Neonatal sepsis) AND (delivery)) AND (Saudi Arabia), TI neonatal sepsis AND TX (birth weight or birth size or fetal weight) AND TI (Saudi Arabia OR Kingdom of Saudi Arabia OR KSA), TI neonatal sepsis AND TX (gestational age) AND TI (Saudi Arabia OR Kingdom of Saudi Arabia OR KSA), and TI neonatal sepsis AND TX (delivery) AND TI (Saudi Arabia OR Kingdom of Saudi Arabia OR KSA).

Selection criteria

Our review included the studies that met the following criteria:

The prevalence, retrospective, and prospective studies

Studies with healthy control groups

Studies provided the number of neonates with sepsis, as well as controls.

Exclusion criteria comprised the following:

Studies with no controls

Non-Saudi population

Data extraction

We used EndNote software to detect and remove duplicates, then all the remaining studies were imported to Rayyan – Qatar Computing Research Institute (QCRI) (Stang. 2010). Selection from the imported studies was primarily done by title and abstract screening utilizing a group of inclusion/exclusion criteria by reviewers to detect studies with relevant findings. Title and abstract screening was followed by full-text assessment of primarily included studies. Data was extracted from studies included in the full-text assessment using a data extraction sheet. Data extracted was related to authors, study year, design, setting, population, participant number, age of participants (age range and mean age), and gender, a diagnostic method for neonatal sepsis, and quantitative data on birthweight, gestational age, and mode of delivery.

Risk of bias assessment

We used the Newcastle-Ottawa scale (NOS) for case-control studies (Ouzzani et al., 2016) to evaluate the quality of studies used for the qualitative and quantitative data synthesis. Any disagreement in the quality assessment was discussed and resolved by the reviewers.

Strategy for data synthesis

Summary tables were provided presenting the collected details from the included studies to produce a qualitative overview of included research features and outcome data. Following completion and assessment of the data processing, the scope for performing the recommended pooled analyzes was assessed. The authors used Review Manager 5.4 (RevMan, 2020) to perform quantitative data synthesis for the case and control data analyses. Fixed-effects meta-analysis was carried out to determine the association between neonatal sepsis and birthweight, gestational age and mode of delivery. Heterogeneity was measured using an I-square statistic (Higgins et al., 2003) as part of the pooled meta-analysis. We could evaluate the publication bias by funnel plot inspection.

3. RESULTS

Search results and characteristics of included studies

A total of 119 articles were extracted from the initial systematic search, and 45 duplicates were removed. Title and abstract screening were implemented on 74 study articles, and 25 studies were excluded. Of all, 49 items underwent full-text assessment, and only 4 studies met the inclusion criteria in this meta-analysis. A summary of the study selection is illustrated in Figure 1. Out of the 4 included studies, one was conducted in Al-Madinah (Al-Mazroea, 2017), one in Abha city (Wahab & Saeed, 2012), one in Al-Khobar city (Dawodu et al., 1997), and one in Taif city (Allam et al., 2015). The total sample size was 491 participants; 223 neonates with sepsis and 200 controls. Summary of study characteristics is presented in Table 1.

Birth weight, gestational age, and mode of delivery as risk factors of neonatal sepsis

Among the factors that enhanced the likelihood of neonatal sepsis incidence, but were not significant in our meta-analysis, comprised birth weight (n=4; SMD -0.68; 95% CI [-0.89, -0.46]) Figure 2. Gestational age have no significant influence on the occurrence of neonatal sepsis (n=3; SMD -0.17; 95% CI [-0.41, -0.06]) Figure 3. This meta-analysis found that the vaginal delivery mode is associated with lower neonatal sepsis incidence (n=3; OR 0.61; 95% CI [0.36, 1.03]) Figure 4. The CS was linked with a greater incidence of neonatal sepsis (n=3; OR2.13; 95% CI [1.23, 3.70]) Figure 5.

Table 1 summary of the features of the involved studies

| Author	Study year	Study design	Population type	Participants number	Sepsis group (n)	Controls (n)	Males (n)	Males (%)	City	Condition	NOS
Al-Mazroea et al. [22]	2017	Case-control	Preterm neonates	80	40	40	35	43.75	Al-Madinah	Neonatal sepsis	6
Wahab Mohamed et al. [23]	2012	Prospective cohort (cross-sectional)	Neonates	102	62	40	46	54	Abha	Early and late onset of neonatal sepsis	7
Dawodu et al. [24]	1997	Case-control	Neonates	104	52	52	62	59.6	Al Khobar	Infants born with septicaemia	8
Allam et al. [25]	2015	Cross-sectional	Neonates	205	69	68	117	57.1	Taif	Neonatal sepsis	7
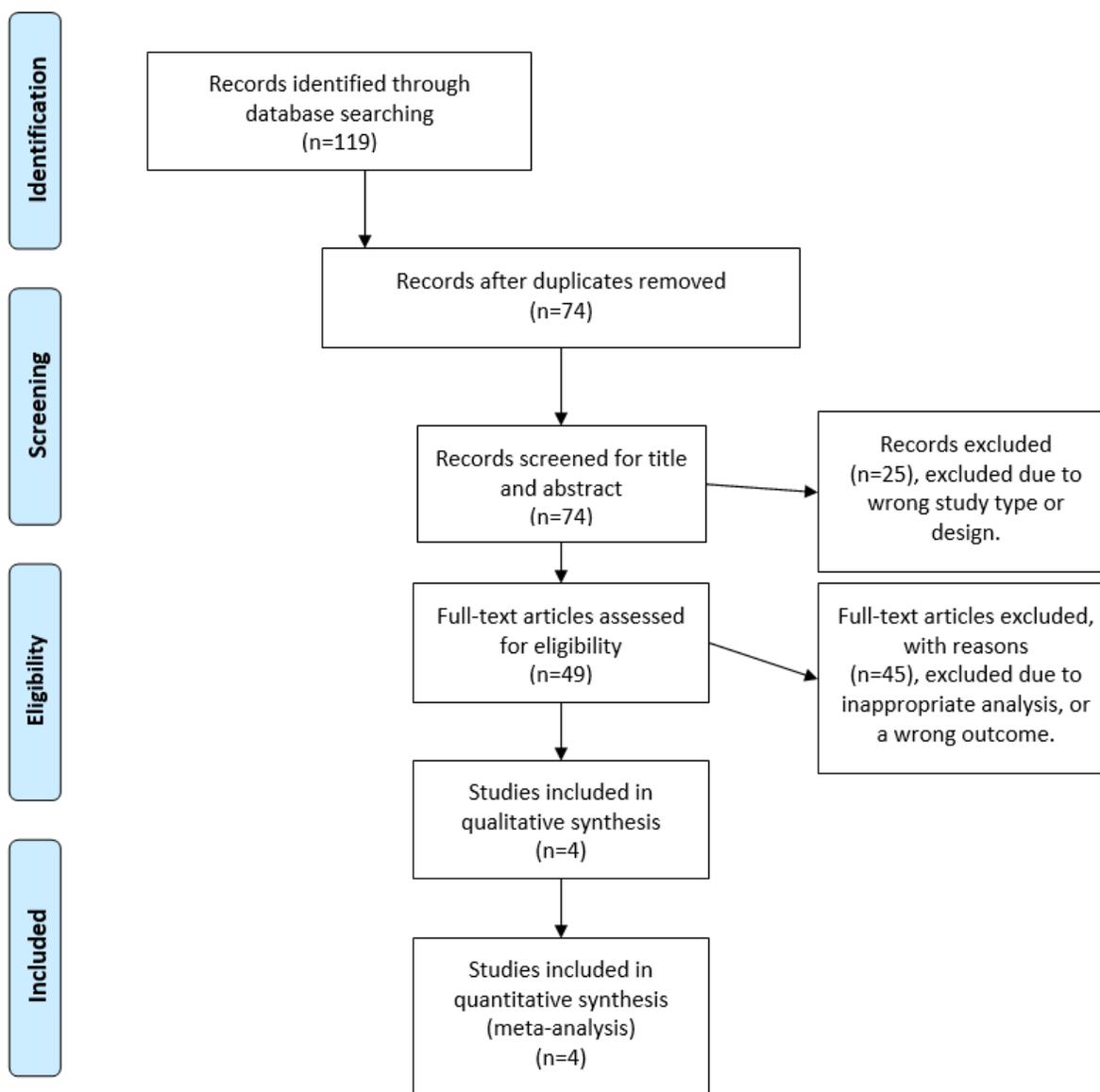
Figure 1 A PRISMA chart presenting the study selection results.
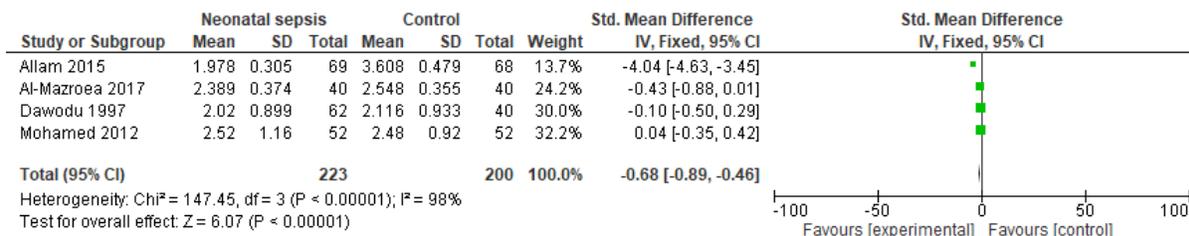
Figure 2 Forest plot presents a fixed-effects meta-analysis of the standardized mean difference of neonates' birth weight with and without sepsis.
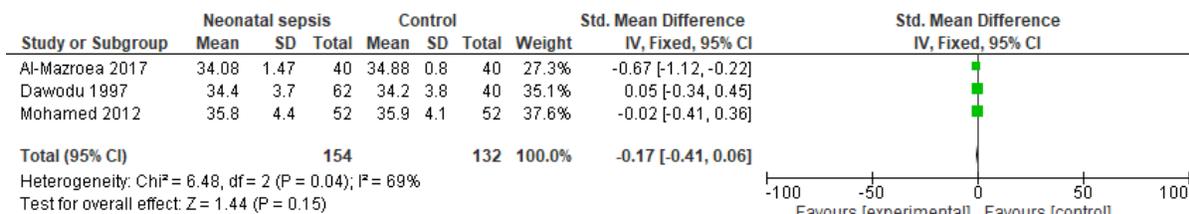

Figure 3 Forest plot presents a fixed-effects meta-analysis of the standardized mean difference of neonates' gestational age with and without sepsis.
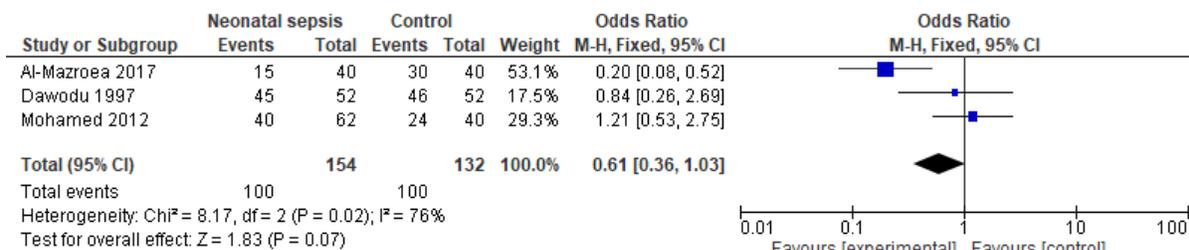

Figure 4 Forest plot showing a fixed-effects meta-analysis of neonates, with and without sepsis, having mothers withvaginal delivery.
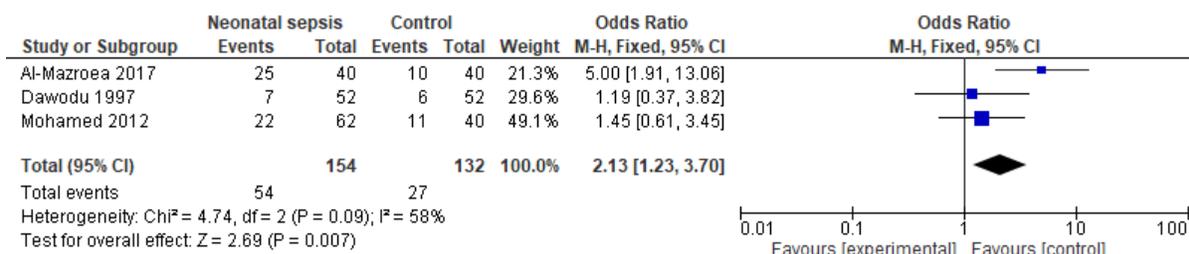

Figure 5 Forest plot showing a fixed-effects meta-analysis of neonates, with and without sepsis, born to mothers who had Cesarean delivery.

Heterogeneity and publication bias

Inspection of funnel plots (Figure 6) reveals symmetrical distribution of the SMDs and ORs obtained from the studies. Significant heterogeneity was found in all analyses of risk factors.
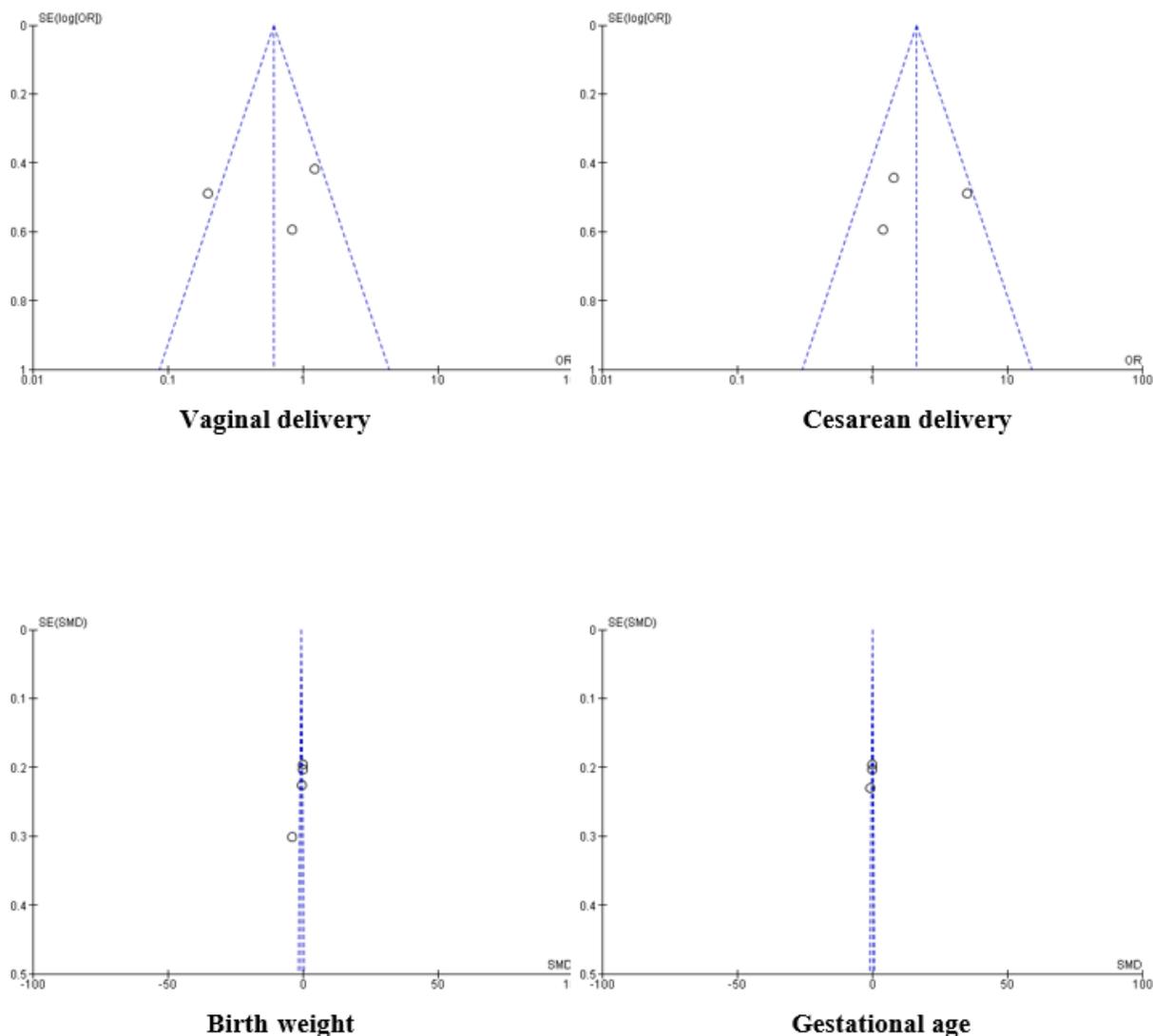
Figure 6 Funnel plots of publication bias for neonatal sepsis risk factors.

4. DISCUSSION

Neonatal sepsis is a critical health problem among neonates and young children. The third Sustainable Development Goal for child health aims to eliminate avoidable mortality of neonates and preschool children by 2030; however, this goal may not be met unless neonatal mortalities directly associated with infection in developed countries are significantly reduced (Ranjeva et al., 2018). This meta-analysis assessed the birth weight, gestational age, vaginal delivery, and CS as neonatal and motherly risk influences of neonatal sepsis.

The current study found that birth weight is not significant in association with neonatal sepsis incidence (n=4; SMD -0.68; 95% CI [-0.89, -0.46]). An included study conducted by Dawodu et al., (1997) reported a significant converse correlation between infant weight at birth and the incidence of septicemia. However, in India, a similar systematic review and meta-analysis were conducted to review and evaluate neonatal sepsis's risk factors. The study found that birth weight (LBW; OR: 7.37, 95% CI: 4.48, 12.1) have a significant effects on initial start of newborn sepsis (Murthy et al., 2019). Stoll et al., (1996) also reported that neonatal sepsis is a significant health problem among very low birth weight neonates. This might be due to low birth weight newborns are extraprobably of being premature, have an immature immune system, are unable to feed, rapidly lose heat, have a low store of glucose, and have the possibility to develop hypoglycemia, which increases the chance of neonatal infections (Leante-Castellanos et al., 2012).

A possible explanation for the insignificant association between birth weight and the danger of newborn sepsis in this Meta-analysis is that most of the former studies included a greater number of studies with more data to interpret. We establish a few eligible studies in Saudi Arabia with a heterogeneity of (I²=99%). Our meta-analysis found that gestational age has insignificant

effect on the frequency of neonatal sepsis (n=3; SMD -0.17; 95% CI [-0.41, -0.06]). Murthy et al., (2019) also found that prematurity was implicated as a significant risk factor on neonatal EOS (OR: 2.05; 95% CI: 1.40, 2.99). A case-control study conducted in Ghana (Adatara et al., 2019) also reported that there is a significant association between premature rupture of membrane and possibility of neonatal sepsis (P<0.001).

Belachew et al., (2020) performed a similar systematic review and meta-analysis in Ethiopia to assess the relationship between neonatal sepsis and gestational age. They reported that preterm neonates were 3.36 times more vulnerable to developing neonatal sepsis than term newborns. The following studies also reported a significant link between gestational age and risk of occurrence of neonatal sepsis in China (Al Kibria et al., 2018), the USA (Simonsen et al., 2014), and Tanzania (Jabiri et al., 2016). The potential interpretation is the immature immune systems of preterm babies (low neutrophil storages). As a result, health professionals who experience invasive management and could liable to hospital acquired infection have the probability to develop neonatal infections. Sepsis causes a quick depletion of bone marrow reserve. Immune replacement therapies are currently being researched for correcting preterm immune deficiencies and preventing neonatal infections. Consequently, staff training and education on infection prevention are important in preventing nosocomial infections (Belachew & Tewabe, 2020).

The present study found that vaginal delivery is associated with a lower incidence of neonatal sepsis (n=3; OR 0.61; 95% CI [0.36, 1.03]); however, cesarean section was linked with a greater risk of occurrence of neonatal sepsis (n=3; OR 2.13; 95% CI [1.23, 3.70]). In contrast, Murthy et al., (2019) reported that vaginal delivery was associated with a greater risk of neonatal sepsis (OR 2.13; 95% CI [0.68, 6.62]). This could be due to newborns delivered by cesarean section were not exposed to the vaginal and fecal bacteria; nonetheless, they often have prolonged stay at the hospital and late breast feeding initiation (Rowe-Murray & Fisher, 2002; Mueller et al., 2015).

Limitations

Since this is a systematic review, we face a lack of sufficient literature that discuss and investigate risk factors, including birth weight, gestational age, and method of delivery among neonates with sepsis, which restricted our research outcomes. Limited available of study articles and small sample size might have an impact on the pooled prevalence. Additionally, using the odds ratio to assess the analyst variables may be influenced by additional confounding variables.

5. CONCLUSION

This systematic review and meta-analysis reported that newborn and mother related influences as potential independent risk factors to have an association with the possibility of newborn sepsis. We also observed that weight of birth, gestational age, besides vaginal delivery are not related to a greater risk of neonatal sepsis, while cesarean delivery was associated with greater risk. We recommend that more investigation and research support our understanding of the occurrence of neonatal sepsis in Saudi Arabia. Also, healthcare personnel developing the care they render to mothers and neonates may be a critical factor in decreasing neonatal sepsis.

Author Contributions
All the authors contributed evenly with regards to data collecting, analysis, drafting and proofreading the final draft.

Conflict of Interest
There are no conflicts of interest.

Data and materials availability
All data associated with this study are present in the paper.

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