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Association of Chorioamnionitis with Neonatal Sepsis and Mortality Rate Among Preterm Infants: A Meta-Analysis

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ABSTRACT

Chorioamnionitis is an intra-amnion infection caused by various pathogens and increases the risk of preterm delivery. This study aims to analyze the association of chorioamnionitis with the incidence of neonatal sepsis and mortality rate among preterm infants. This systematic review and meta-analysis was conducted based on PRISMA guideline. All studies which evaluated chorioamnionitis with the incidence of neonatal sepsis and mortality rate among preterm infants were included in this study. We limited our search to 2001-2020. A total of 34 articles were screened. Nine cohorts were included according to inclusion criteria. Based on statistical analysis, chorioamnionitis was associated with the incidence of early-onset sepsis (OR=3.45; 95%CI=2.02-5.89; p < 0.00001). Chorioamnionitis had a protective effect toward late-onset sepsis (OR=0.82; 95%CI=0.71-0.93; p=0.003) and not associated with mortality rate among preterm infants (OR 0.75; 95%CI=0.54-1.04; p=0.09). Chorioamnionitis was associated with higher risks of early-onset sepsis and lower risks of late-onset sepsis. However, the mortality rate among preterm infants with early-onset sepsis was not associated with chorioamnionitis.

Keywords: chorioamnionitis; neonatal sepsis; early-onset sepsis; late-onset sepsis; mortality; premature

INTRODUCTION

Preterm delivery is defined as a delivery that occurs before 37 weeks of pregnancy. Several factors including the maternal, fetus, and chorionic membrane abnormality increase the risk of premature delivery.[1] The incidence of preterm delivery varied among countries. Generally, about 5-18% of all delivery were preterm delivery.[2] Eighty-five percent of these cases occurred in African and Asian countries.[3,4]

Chorioamnionitis is an intra-amnion infection caused by various pathogens and increases the risk of preterm delivery.[5] Clinical manifestations of chorioamnionitis include fever, increased maternal and fetal heart rate, and purulent amniotic fluid with a foul odor. Physical examination, such as abdominal tenderness on palpation, supports the diagnosis of chorioamnionitis, yet abdominal pain due to uterus contractions often masks this finding. The laboratory works in chorioamnionitis cases are blood tests (leukocytosis and increased C-reactive protein), microbial culture, and histological examination.[5]

Prematurity is associated with short-term complications resulting in multiple organs immaturity, neurons development impairment (cerebral palsy), intellectual disability, and visual and hearing disorders.[2] Many detrimental clinical outcomes are related to prematurity, namely respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage, neurologic sequelae, and neonatal sepsis.[6] Concerning neonatal sepsis, rupture of the membrane for more than 24 hours increases the risk of sepsis by 2-10 folds.[7]

Previous studies had explored the association of chorioamnionitis with preterm delivery and numerous complications, yet the results were inconsistent. This meta-analysis aims to analyze the association of chorioamnionitis with the incidence of neonatal sepsis and the mortality rate among preterm infants with early-onset sepsis.

METHODS

This systematic review and meta-analysis included all prospective and retrospective cohort studies. The literature search was performed systematically on PubMed and Google Scholar databases to identify any relevant articles. All data were narratively processed to analyze the association of chorioamnionitis with the incidence of neonatal sepsis and mortality rate among preterm infants. The inclusion decision of the study was based on the availability of the data and the validity of the measurement methods.

The detailed literature search process was reported under preferred reporting items for systematic review and meta-analysis (PRISMA) protocol. The methodological quality of the included studies was assessed based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklists.

All collected data were analyzed using the meta-analysis method which combines statistical results from similar studies to answer the research question and presented in forest plots. All statistical analyses in this study were carried out using Review Manager 5.4.

RESULTS

Based on the literature search, there were 34 initial studies. After the screening process, only 9 studies were included based on data availability and measurement method validity.

Maternal data included the history of fever (>38°C) preceding delivery, latest leukocyte count, positive urine culture as an indicator of urinary tract infection during the pregnancy period, history and duration of premature rupture of membrane, finding of group beta streptococcus on the vaginal swab, foul odor amniotic fluid, and tachycardia. While neonatal data included weeks of pregnancy, leukocytes count, platelet count, C-reactive protein, and any findings of pathogens.

The data was extracted and collected on Cochrane's collection sheets with modification. The collected data was composed of authors, title, study location, sample, study design, the incidence of chorioamnionitis, incidence of early-onset sepsis (EOS), incidence of late-onset sepsis (LOS), and mortality rate among preterm infants. The results are presented in Table 1.

TABLE 1: Characteristics of the study

No.	Location	Title, Authors, and Year of publication	Sample	Study design	Statistical analysis	Assessment	Results
1.	USA	*Risk of Early-Onset Sepsis following Preterm, Prolonged Rupture of Membranes with or without Chorioamnionitis* (Gaston Ofman *et al.*, 2016)[8]	2.192 infants	Retrospective cohort	Mann–Whitney U-test, chi-square test, Fisher exact test, and ANOVA	1. The risk of EOS among infants without exposure to preterm premature rupture of membrane (PPROM) and chorioamnionitis. 2. The risk of EOS among infants with exposure to PPROM, but no chorioamnionitis. 3. The risk of EOS among infants with exposure to PPROM and chorioamnionitis.	1. 750 infants (80%) were not exposed to PPROM and chorioamnionitis (group 1) 2. 381 infants (17%) were exposed to PPROM, but not to chorioamnionitis (group 2) 3. 61 infants (3%) were exposed to both PPROM and chorioamnionitis (group 3) 4. The incidence of EOS was not different between group 1 and 2 (5.4 vs 5.5%, p=0.86) 5. Group 3 had the highest EOS incidence (24.6%) among groups with an OR of 4.1 (95%CI=2.83–5.30, p < 0,001).
2.	Canada	*Effect of Clinical and Histological Chorioamnionitis on the Outcome of Preterm Infants* (Nehad Nasef *et al.*, 2013)[9]	274 infants	Retrospective cohort	Chi-square test and Fisher exact test	Incidence of EOS and mortality rate based on clinical and histological chorioamnionitis	1. The incidence of EOS based on clinical chorioamnionitis was 9% (OR=0.3, 95%CI=0.06–1.9, p= 0.24) 2. The incidence of EOS based on histological chorioamnionitis was 4% (OR=0.7, 95%CI=0.16–3.7, p= 0.7) 3. The mortality rate among clinical chorioamnionitis was 12% (OR=0.6, 95%CI=0.1-2.1, p= 0.47) 4. The mortality rate among clinical chorioamnionitis was 16% (OR=0.8, 95%CI=0.3-1.7, p= 0.59) 15 (16%).
3.	Taiwan	*Impact on Neonatal Outcome and Anthropometric Growth in Very Low Birth Weight Infants with Histological Chorioamnionitis* (Shu-Chi Mu *et al.*, 2008)[10]	64 mothers	Prospective cohort	Independent t-test and Pearson's	Association of histological chorioamnionitis with the incidence of neonatal sepsis	1. The incidence of sepsis was 32.8% (aOR=3.355, 95%CI=1.275-8.827, p = 0.016) 2. The incidence of RDS was 87.5% (aOR=2.068, 95%CI=0.768-5.573, p= 0.061) 3. The incidence of BPD was 39.1% (a OR=3.018, 95%CI=1.235-7.378, p= 0.016)
4.	Japan	*Impact of chorioamnionitis on short- and long-term outcomes in very low birth weight preterm infants: the Neonatal Research Network Japan* (Ken Miyazaki et al., 2016)[11]	1235 infants	Retrospective cohort	Chi-square test and t-test	Short- and long-term effects of histological chorioamnionitis	1. The incidence of sepsis was 14.1% (OR=1.71, 95%CI=1.33-2.20, p <0.001) 2. The incidence of RDS was 54.7% (OR=0.54, 95%CI=0.45-0.64, p <0.001) 3. The mortality rate was 10.4% (OR=0.97, 95%CI=0.73-1.29, p= 0.84)

No.	Location	Title, Authors, and Year of publication	Sample	Study design	Statistical analysis	Assessment	Results
5.	Pakistan	*Neonatal sepsis following prolonged rupture of membranes in a tertiary care hospital in Karachi, Pakistan (*Muhammad Matloob Alam *et al*., 2014)[12]	428 infants	Retrospective cohort	Chi-square test and Fisher exact test	Association of PROM (>48 hours) and chorioamnionitis with incidence of EOS	1. The incidence of EOS in infants exposed to PROM was 41% (crude OR=9.6, 95%CI=3.3-27.1; aOR=8.2, 95%CI=0.7-98.2, p < 0.001) 2. The incidence of EOS in infants exposed to Chorioamnionitis was 71% (crude OR=59.3, 95%CI=18.6-188.4; aOR=4.1, 95%CI=0.6-26.8, p< 0.001)
6.	Spain	*Outcomes of Very-Low-Birth-Weight Infants Exposed to Maternal Chorioamnionitis: A Multicentre Study* (Fermín García- Muñoz Rodrigo et al., 2014)[13]	1.480 infants	Retrospective cohort		Association of chorioamnionitis with morbidity and mortality among very-low-birth-weight (VLBW) infants	1. Association with EOS was significant with aOR of 3.102 (95%CI=2.306-4.173, p<0.001) 2. Association with LOS was significant with aOR of 0.849 (95%CI=0.729–0.989, p=0.035) 3. Association with LOS was not significant with aOR of 0.861 (95%CI=0.723–1.026, p=0.095) 4. Association with BPD was not significant with aOR of 0.949 (95%CI=0.745–1.207, p=0.668) 5. 5. Association with mortality rate was not significant with aOR of 0.807 (95%CI=0.647– 1.007, p=0.058)
7.	Australia	*Histologic Chorioamnionitis Is Associated With Reduced Risk of Late-Onset Sepsis in Preterm Infants* (Tobias Strunk, et al., 2012)[14]	303 infants	Retrospective cohort	Chi-square test and Fisher exact test	Association of histological chorioamnionitis with EOS and LOS among preterm infants	1. Association with EOS was significant with an OR of 2.31 (95%CI=1.03–5.15, p=0.036) 2. Association with LOS was not significant with an OR of 0.75 (95%CI=0.56–1.00, p=0.051)
8.	Canada	*Outcome of Neonates Less Than 30 Weeks Gestation with Histologic Chorioamnionitis* (E. Dempsey, et al., 2005)[15]	392 infants	Retrospective cohort	T-test and Mann-Whitney-U-test	Clinical outcome of preterm infants exposed to maternal histologic chorioamnionitis	1. Association with sepsis was significant with an OR of 6.9 (95%CI=2.2–20, p=0.001) 2. Association with RDS was significant with an OR of 0.43 (95%CI=0.26–0.71, p=0.001) 3. Association with BPD was not significant with an OR of 1.24 (95%CI=0.43–2.5, p=0.8) 4. Association with mortality rate was significant with an OR of 0.38 (95%CI=0.2-0.74, p=0.005)
9.	South Korea	*The Association of Histological Chorioamnionitis and Antenatal Steroids on Neonatal Outcome in Preterm Infants Born at Less than Thirty-Four Weeks' Gestation* (Hye Mi Ahn, et al., 2012)[16]	89 infants	Retrospective cohort	Chi-square test and Fisher exact test	Association of chorioamnionitis with the incidence of sepsis, morbidity, and mortality rate among VLBW infants	1. Association with EOS was not significant with an OR of 2.5 (95%CI=0.26–23.99, p=0.427) 2. Association with LOS was not significant with an OR of 0.32 (95%CI=0.10–1.05, p=0.059) 3. Association with RDS was not significant with an OR of 0.91 (95%CI=0.33–2.56, p=0.864) 4. Association with BPD was significant with an OR of 0.18 (95%CI=0.05-0.63, p=0.007)

Nine studies explored the association of chorioamnionitis with EOS among preterm infants. Based on forest plot analysis (Figure 1.), the association was significant with a combined OR was 3.45 (95%CI=2.02-5.89, p < 0.00001)

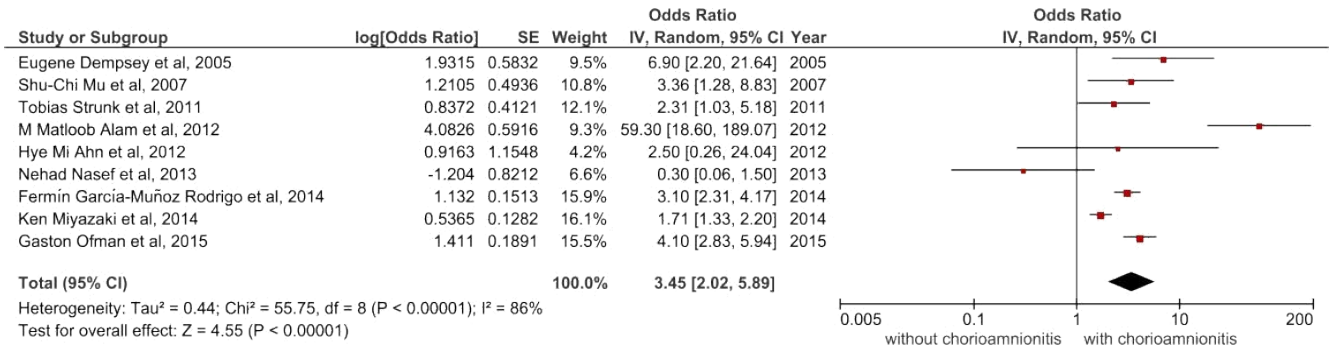

FIGURE 1: The association of chorioamnionitis with EOS among preterm infants

Three studies reported LOS outcomes among preterm infants. The forest plot analysis (Figure 2.) demonstrated a significant association between chorioamnionitis with LOS (OR=0.82, 95%CI=0.71-0.93, p = 0.003)

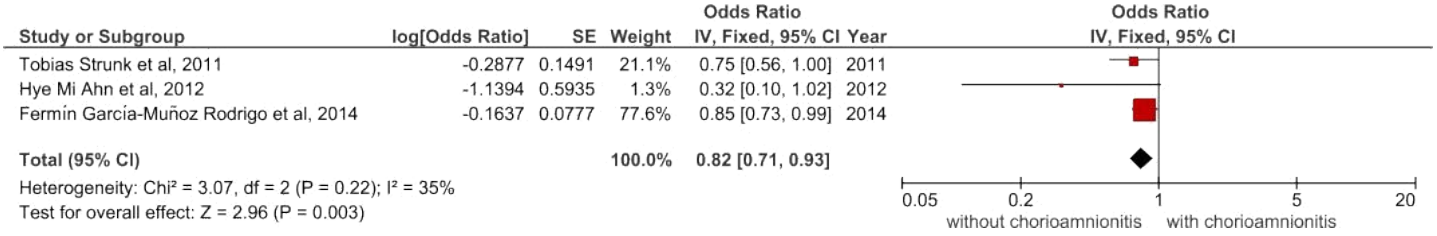

FIGURE 2: The association of chorioamnionitis with LOS among preterm infants

The association between chorioamnionitis and mortality rate among preterm infants with EOS was evaluated in 4 studies.

The mortality rate was not associated with chorioamnionitis as the OR was 0.75 with 95%CI ranging from 0.54 to 1.04 and a p-value of 0.09 (Figure 3.).

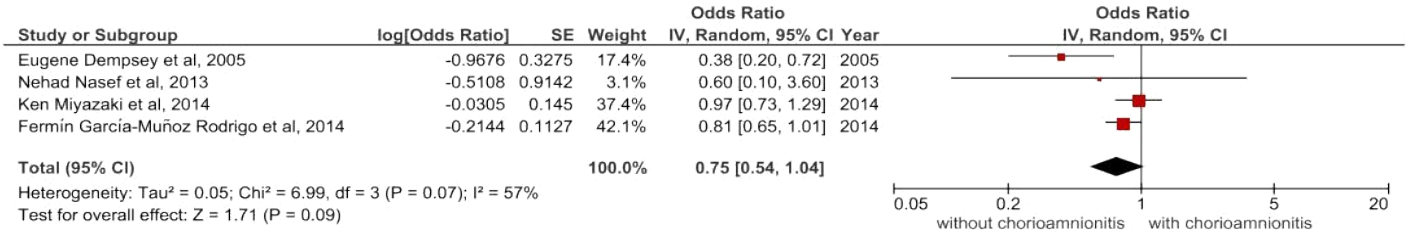

FIGURE 3: The association of chorioamnionitis with the mortality rate

DISCUSSION

Chorioamnionitis or intra-amnion infection is defined as acute inflammation of the chorion and placental membrane due to ascending infection during rupture of the membrane. Chorioamnionitis is a common complication during pregnancy, yet associated with detrimental outcomes, such as postpartum infection, maternal sepsis, fetal death, preterm delivery, neonatal sepsis, chronic pulmonary disorder, cerebral palsy, and neurological impairments.[17]

Neonatal sepsis is divided into two groups, early-onset sepsis (EOS) and late-onset sepsis (LOS).[18] EOS generally defined as sepsis with evidence of bacteremia or bacterial meningitis which occurs in neonates within 72 hours of treatment in NICU. EOS often occurs during the first 72 hours of life in preterm infants due to vertical infection from their mother during delivery.[18] While, LOS is sepsis in neonates after 72 hours of treatment in NICU due to vertical or horizontal infection.[19,20]

As stated before, vertical infection is the culprit of EOS. The pathogens colonize in the maternal genitourinary tract and mobilize to the membrane during or right before the delivery process, resulting in intra-amniotic infection.[5] Both mothers and infants have several risk factors in developing EOS. The maternal risk factors include diet pattern (consuming Listeria monocytogenes contaminated food during or right before delivery), interventions involving nearby membrane structures including cervical cerclage and amniocentesis, streptococcus group B colonization, and bacteriuria.[21] In addition, maternal immune response plays a crucial role in the development of neonatal sepsis. Maternal IgG antibody response to polysaccharides of streptococcus group B has a protective effect on pathogens related to EOS after exposure to chorioamnionitis.[22] The risk of EOS increases by 1% when the membrane ruptures for more than 18 hours before delivery and 1-4% when the infants were exposed to chorioamnionitis.[21–23]

Neonatal risk factors of EOS include prematurity, low birth weight, congenital disease, delivery complication, and low APGAR score (scored 6 during the first 5 minutes). An inadequate immune system along with a low level of transplacental maternal IgG also increases the risk of neonatal sepsis.[24] The function of skin and mucosal tissue as a barrier is not optimal among preterm infants, therefore invasive procedures such as intravenous cannulation and intubation could trigger the pathogens to enter the bloodstream. Socio-environment aspects are also associated with neonatal sepsis. Delayed prenatal treatment, low socio-economic status, low maternal nutritional status, drugs and another addictive usage, male infants, and Afro-American race increase the risk of neonatal sepsis.[25,26]

Nine studies explored the association between chorioamnionitis with EOS and were included in this meta-analysis. Based on forest plot analysis, the combined effect was significant with an OR of 3.45 (95% CI 2.02-5.89, $p < 0.00001$). A study in 2019 also demonstrated a similar result in which sepsis was 3-folds more frequent among infants exposed to chorioamnionitis. The study also reported that 6.6% of infants developed EOS which 0.2% were confirmed and the other 6.4% were presumed sepsis. The incidence of EOS was lower following gestational age (30.2% in preterm vs 4.2% in aterm infants).[27] Another study also reported the association between chorioamnionitis with EOS. Unadjusted data demonstrated a strong association with OR of 4.29, 95% CI 3.63–5.06, yet this association was lowered after adjustment (OR 2.51, 95% CI 1.51–4.14).[28]

The growing theory explained the relation between immunomodulatory activity to infection or intrauterine inflammation with the development of EOS, yet the exact mechanism of these theories is still unclear.[28] Maternal genito-urinary tract is expected to be the main source of pathogens in sepsis. If the infection or intra-uterine inflammation is chronically active, leukocyte infiltration will occur and trigger the production of inflammation cytokine (IL-1β, IL-4, IL-6, IL-8, and IL-18) dan chemokine (IL-8, CXCL6, and CXCL10). As consequence, the Interleukin 1 Receptor Associated Kinase 1 (IRAK-1) pathway is activated, causing fetal inflammatory response syndrome (FIRS). The FIRS is closely related to detrimental clinical outcomes, namely EOS among preterm infants.[29]

Late-onset sepsis is a type of sepsis occurring after 72 hours of treatment in the NICU. LOS is commonly caused by nosocomial infection of negative coagulase Staphylococcus. Neonatal immune responses to maternal infection are dependent on the maturity and function of their immune system.[30] As FIRS develops, the IL-6 in the plasma and polymorphonuclear leukocytes in the placenta will increase.[31] LOS in preterm infants is associated with longer intra-hospital days of treatment, higher morbidity, and higher mortality rate. The risk factors of LOS include low birth weight, preterm delivery, pathogens exposure, poor hygiene, and central vein cannulation.

In this study, three studies reported the association between chorioamnionitis with the incidence of LOS. The combined effect in forest plot demonstrated significant statistics with OR of 0.82 (95%CI= 0.71-0.93, p= 0.003). This result indicated that exposure to chorioamnionitis had a protective effect on developing LOS among premature infants. The latest study reported similar results in which the incidence of LOS was lower in infants who were exposed to histological chorioamnionitis.[14] The study included 838 infants with gestational age below 30 weeks and concluded that histological chorioamnionitis increases the risk of EOS (OR=2.31, 95%CI=1.03–5.15, p = 0.036), yet lowers the risk of LOS (HR=0.97, 95%CI=0.75–1.24, p = 0.562).

The authors hypothesized that chorioamnionitis only causes inflammation which promotes the maturity process of the immune system involving the placenta.

While the exact mechanism is yet to be clear, some possible explanations are pathogens ligand transfer and/or maternal immune mediator through the placenta. The activation of the immune system through perinatal inflammation promotes the development of immune components with a longer lifespan.[32] Higher plasma level of pro-inflammatory cytokine in the placenta is related to a lower risk of allergy. While perinatal inflammation is associated with a lower risk of LOS and chronic lung disease, this inflammation is also related to the incidence of cerebral palsy.[33]

Another study reported the influence of intrauterine inflammation on LOS. The study concluded no relationship between intrauterine inflammation with the incidence of LOS. In addition, intrauterine inflammation was not associated with the neonatal immune response which is responsible for preventing LOS.[34] A recent meta-analysis also supports this conclusion. The meta-analysis stated that chorioamnionitis is a protective risk to LOS, yet after gestational age adjustment, there was no significant association.[28]

Studies on the animal model showed intrauterine inflammation induced by lipopolysaccharide (LPS) would significantly increase neutrophil, monocytes, and lymphocytes count, followed by the synthesis of abundant anti-inflammation cytokine.[35,36] However, after repeated LPS administration, the synthesis was suppressed, suggesting a tolerance response to stimuli.[37] This mechanism may explain why intrauterine inflammation is not related to LOS among preterm infants. Another plausible explanation is that intrauterine inflammation is not adequate to induce the immune response responsible for preventing LOS. An in vitro study reported that exposure of endotoxin to neonatal immune cells significantly reduced pro-inflammatory cytokine expression of T-helper and T-helper 2 cells, compared to mature immune cells.[37] Aterm infants who were exposed to Bacillus Calmette-Guérin (BCG) showed a similar response of TNF-α and IL-6 to adults.

In this meta-analysis, four studies were included and combined effects demonstrated no significant association between chorioamnionitis and mortality rate among preterm infants with EOS (OR=0.75, 95%CI= 0.54-1.04, p=0.09). On the contrary, an early study in 1987 stated that chorioamnionitis increases the risk of perinatal death, especially those in preterm or extremely preterm infants.[38] This higher mortality rate might be associated with funisitis or FIRS.[39,40] Growing theory stated that the mortality rate is dependent on the histological feature of chorioamnionitis and funisits.[41]

CONCLUSION

Chorioamnionitis is associated with a higher incidence of EOS and a lower incidence of LOS. There was no association between chorioamnionitis with a mortality rate among preterm infants with EOS.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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None to disclose

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