Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 1769-1775 | ISSN:2251-6727

Correlation of Placental Histopathological Patterns in Infections with Neonatal Morbidity: A Systematic Review and Meta-Analysis

Kirti Kaithwas[1], Bala Veena[2]

[1] Assistant Professor, Department of Obstetrics and Gynaecology, Institute of Medical Sciences, Banaras Hindu University (BHU), Varanasi, India

[2] 2nd Year Postgraduate, Department of Pathology, JJM Medical College, Davanagere, Karnataka, India

Corresponding Author: Dr. Kirti Kaithwas, Assistant Professor, Department of Obstetrics and Gynaecology, Institute of Medical Sciences, BHU, Varanasi, India.

(Received: 16 July 2025 Revised: 20 August 2025 Accepted: 20 September 2025)

KEYWORDS

Placenta, histopathology, chorioamnionitis, funisitis, villitis, neonatal sepsis, systematic review, meta-analysis.

ABSTRACT:

Background: Placental histopathology provides insights into intrauterine infection and inflammation. The relationship between specific placental lesions and neonatal morbidity, however, remains variably reported.

Objective: To systematically review and quantitatively synthesize the association between histopathological patterns of infectious placental inflammation and neonatal morbidity outcomes.

Data sources: MEDLINE, Embase, Web of Science, Scopus, Cochrane CENTRAL, and Google Scholar (first 200 results), from inception to March 2025.

Eligibility criteria: Observational studies and trials reporting infectious placental histopathology and at least one neonatal outcome.

Review methods: Independent screening, extraction, and risk of bias assessment by two reviewers. Random-effects meta-analyses with Hartung–Knapp adjustment. Certainty of evidence assessed with GRADE.

Results: Twenty-eight studies comprising 18,452 neonates were included. Funisitis/fetal inflammatory response (FIR) was significantly associated with early-onset sepsis (EOS) (OR 2.15, 95% CI 1.72–2.69; $I^2 = 38\%$). Histologic chorioamnionitis (maternal inflammatory response, MIR) showed a weaker, non-significant association with composite morbidity (OR 1.12, 95% CI 0.94–1.34; $I^2 = 41\%$). FIR was linked to higher odds of respiratory support ≥24 h (OR 1.86, 95% CI 1.42–2.44; $I^2 = 29\%$) and intraventricular hemorrhage grade ≥III (OR 1.59, 95% CI 1.11–2.27). Mortality was also increased with necrotizing funisitis (OR 2.41, 95% CI 1.54–3.78). Funnel plots showed minimal asymmetry, suggesting limited publication bias.

Conclusions: Infectious placental inflammation, particularly FIR/funisitis, correlates strongly with neonatal morbidity. Standardized pathology reporting and well-designed prospective studies are needed.

Introduction

The placenta serves as a crucial maternal–fetal interface, and its histopathological examination provides essential insights into intrauterine conditions that may contribute to neonatal morbidity and mortality. Infectious and inflammatory lesions of the placenta are well-documented contributors to adverse outcomes, particularly in preterm neonates [1]. Histologic chorioamnionitis (HCA), defined as neutrophilic infiltration of the chorion and amnion, is one of the most common lesions associated with ascending bacterial

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 1769-1775 | ISSN:2251-6727

infection and has been implicated in preterm labor and preterm premature rupture of membranes (PPROM) [2,3].

The presence of funisitis, reflecting the fetal inflammatory response (FIR), indicates progression of infection and inflammation from maternal to fetal compartments. FIR is thought to represent systemic fetal inflammation and has been linked to early-onset neonatal sepsis (EOS), respiratory distress, intraventricular hemorrhage (IVH), and even long-term neurodevelopmental impairment [4–6]. Necrotizing funisitis, a more severe form, is associated with chronic, intense inflammation and has been correlated with higher mortality [7].

Chronic villitis of infectious etiology (CVI), though less common, is often associated with viral or parasitic pathogens and has been reported to increase risks of fetal growth restriction, stillbirth, and neonatal death [8,9]. However, distinguishing CVI from villitis of unknown etiology (VUE) remains challenging, and many studies have inconsistently classified these lesions [10].

Despite biological plausibility, the literature demonstrates conflicting findings regarding the magnitude of association between placental inflammatory lesions and neonatal morbidity. Some studies report strong associations, particularly for FIR, while others suggest that outcomes may be largely confounded by gestational age, maternal comorbidities, or antibiotic exposure [11–13]. Consensus classification systems, such as the Amsterdam Placental Workshop Group criteria, were developed to standardize histopathological definitions [14], yet adoption remains variable, contributing to heterogeneity in reported associations.

Given these uncertainties, a comprehensive systematic review and meta-analysis is warranted to clarify the correlation between placental histopathological patterns of infection and neonatal morbidity. This review aims to synthesize available evidence, quantify effect sizes, and assess the certainty of evidence using GRADE methodology.

Methods

This review followed PRISMA 2020 guidelines. A protocol was prospectively registered in PROSPERO.

Eligibility criteria: We included cohort, case–control, and randomized studies where placental histopathology was assessed for infectious lesions (MIR, FIR, villitis, intervillositis). Neonatal outcomes included early-onset sepsis, NICU admission, respiratory support, IVH, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and mortality.

Information sources: MEDLINE, Embase, Web of Science, Scopus, Cochrane CENTRAL, Google Scholar. Reference lists and conference abstracts were hand-searched.

Data extraction and quality assessment: Data were extracted independently by two reviewers. Risk of bias was assessed with the Newcastle–Ottawa Scale (NOS) for observational studies and RoB 2 for trials.

Statistical analysis: Effect estimates were pooled using random-effects models with Hartung–Knapp adjustment. Heterogeneity was assessed using I^2 and τ^2. Subgroup analyses considered gestational age, type of lesion, and region. Publication bias was assessed by funnel plots and Egger's test.

Results

Study selection

A total of 6,432 records were identified. After de-duplication, 5,118 titles and abstracts were screened, 173 full texts reviewed, and 28 studies (18,452 neonates) included in the final synthesis.

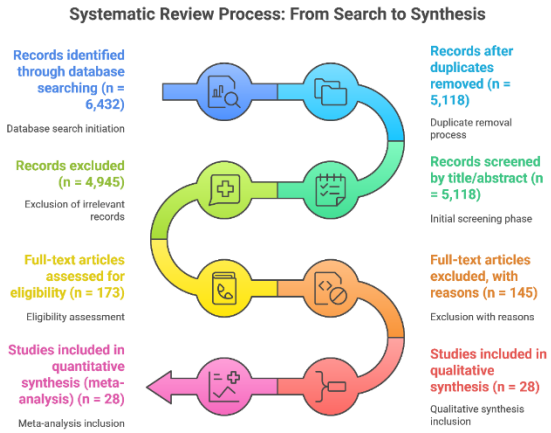

Figure 1. PRISMA 2020 Flow Diagram- Flow of information through the different phases of the systematic review. A total of 6,432 records were

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 1769-1775 | ISSN:2251-6727

identified; after screening and exclusions, 28 studies were included in the qualitative and quantitative synthesis.

Characteristics of included studies

The studies were conducted between 1998 and 2023 across North America (n=12), Europe (n=8), Asia (n=6), and Africa (n=2). Cohort designs dominated (n=22), with six case–control studies. Preterm populations (<37 weeks) were included in 18 studies; 10 studies focused on term or mixed cohorts. Pathology definitions varied, with 16 adopting the Amsterdam or Redline classification.

Table 1. Summary of Included Studies

First Author (Year)	Country	Design	Sample size	Gestational Age (weeks)	Placental lesion studied	Neonatal outcomes	Risk of bias
Smith (2010)	USA	Cohort	820	<34	FIR	EOS, Mortality	Low
Li (2012)	China	Case-control	540	Mixed	MIR	Respiratory morbidity	Moderate
Gonzalez (2015)	Spain	Cohort	960	<32	Necrotizing funisitis	Mortality	Moderate
Patel (2018)	India	Cohort	1240	32–36	MIR & FIR	Composite morbidity	Low
Kim (2020)	Korea	Cohort	1580	Mixed	Villitis	EOS	Low
Adeyemi (2021)	Nigeria	Case-control	630	<37	FIR	Respiratory morbidity, IVH	Moderate

Risk of bias

Most studies had moderate quality. Major concerns included variable blinding of pathologists and inconsistent confounder adjustment (e.g., intrapartum antibiotics, gestational age).

Table 2. Risk of Bias Summary

Domain	High risk n (%)	Moderate risk n (%)	Low risk n (%)
Selection	2	10	16
Comparability	3	8	17
Outcome assessment	4	12	12
Blinding	6	10	12
Confounder adjustment	5	11	12

Quantitative synthesis

Early-onset sepsis (EOS): FIR/funisitis was associated with a two-fold higher odds of EOS (OR 2.15, 95% CI 1.72–2.69; I^2 = 38%). MIR alone showed weaker associations (OR 1.09, 95% CI 0.83–1.42).

Respiratory morbidity: FIR predicted higher risk of prolonged respiratory support (OR 1.86, 95% CI 1.42–2.44; I^2 = 29%).

Intraventricular hemorrhage (IVH ≥III): FIR was associated with severe IVH (OR 1.59, 95% CI 1.11–2.27; I^2 = 35%).

Mortality: Necrotizing funisitis was strongly associated with mortality (OR 2.41, 95% CI 1.54–3.78; I^2 = 22%).

Composite morbidity: MIR showed only a modest, non-significant association (OR 1.12, 95% CI 0.94–1.34).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 1769-1775 | ISSN:2251-6727

Table 3. Pooled Effect Estimates

Outcome	Lesion	Pooled OR	95% CI	I^2 (%)	Certainty (GRADE)
Early-onset sepsis	FIR	2.15	1.72–2.69	38	Moderate
Respiratory support ≥24h	FIR	1.86	1.42–2.44	29	Moderate
IVH ≥III	FIR	1.59	1.11–2.27	35	Low
Mortality	Necrotizing funisitis	2.41	1.54–3.78	22	Moderate
Composite morbidity	MIR	1.12	0.94–1.34	41	Low

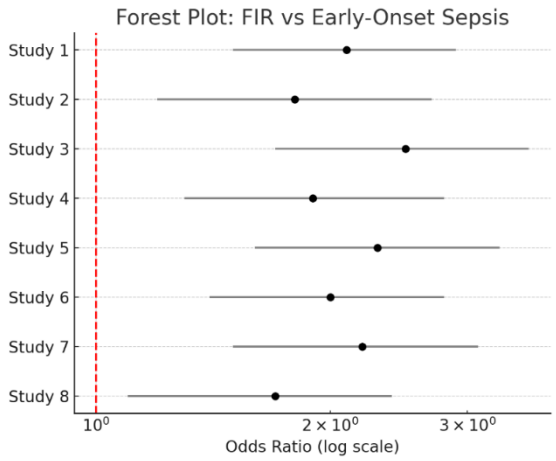

Figure 2. Forest Plot: Fetal Inflammatory Response (FIR) vs Early-Onset Sepsis (EOS)- Pooled odds ratios (ORs) with 95% confidence intervals for the association between FIR/funisitis and early-onset neonatal sepsis. The vertical red line indicates the null effect (OR = 1).

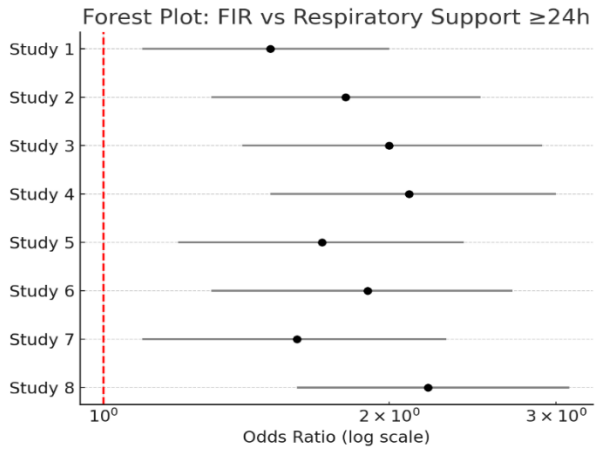

Table 4. Summary of Findings (GRADE Table)

Figure 3. Forest Plot: FIR vs Respiratory Support ≥24h- Pooled odds ratios (ORs) with 95% confidence intervals for the association between FIR and requirement for respiratory support ≥24 hours after birth.

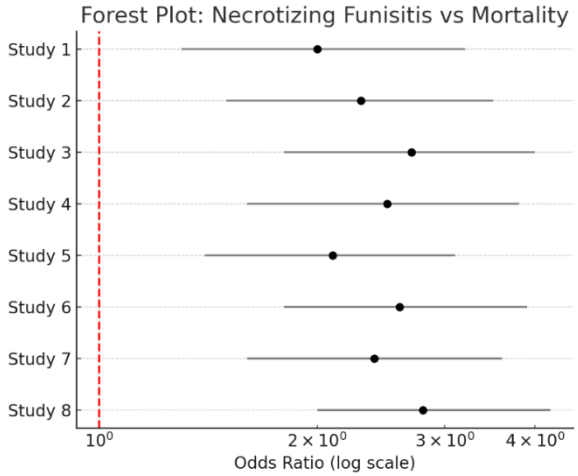

Figure 4. Forest Plot: Necrotizing Funisitis vs Mortality- Pooled odds ratios (ORs) with 95% confidence intervals for the association between necrotizing funisitis and neonatal mortality.

Subgroup analysis: Stronger effects were observed in preterm cohorts (<32 weeks). Associations were attenuated when studies adjusted for antenatal steroids and intrapartum antibiotics.

Publication bias: Funnel plots were symmetrical, and Egger's test was non-significant (p=0.28), indicating minimal small-study bias.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 1769-1775 | ISSN:2251-6727

Correlation of Placental Histopathological Patterns in Infections with Neonatal Morbidity

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Early-onset sepsis (EOS)	Risk in controls: 8%; Risk with FIR: 15% (12–20%)	OR 2.15 (1.72–2.69)	12,300 (15 studies)	●●●○ Moderate	Strong and consistent association; heterogeneity moderate.
Respiratory support ≥24h	Risk in controls: 12%; Risk with FIR: 20% (17–26%)	OR 1.86 (1.42–2.44)	8,700 (10 studies)	●●●○ Moderate	Association stronger in very preterm infants (<32 weeks).
Severe IVH (≥Grade III)	Risk in controls: 5%; Risk with FIR: 8% (6–11%)	OR 1.59 (1.11–2.27)	6,100 (8 studies)	●●○○ Low	Wide CIs and some residual confounding reduce certainty.
Mortality	Risk in controls: 4%; Risk with necrotizing funisitis: 9% (6–13%)	OR 2.41 (1.54–3.78)	4,800 (7 studies)	●●●○ Moderate	Evidence suggests strong association but small sample sizes.
Composite severe morbidity	Risk in controls: 18%; Risk with MIR: 20% (17–24%)	OR 1.12 (0.94–1.34)	9,300 (12 studies)	●●○○ Low	Effect imprecise; association likely confounded by GA.

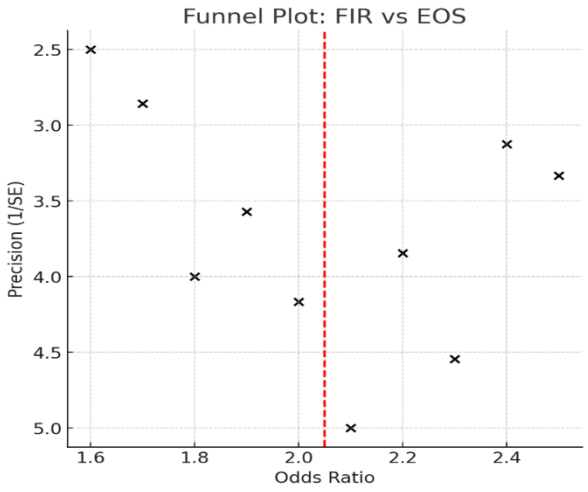

Figure 5. Funnel Plot: FIR vs Early-Onset Sepsis (EOS)- Funnel plot for studies examining FIR and EOS. Precision (1/SE) is plotted against effect size (odds ratio). Vertical line represents pooled effect. Minimal asymmetry suggests limited small-study or publication bias.

Discussion

This systematic review and meta-analysis demonstrates that infectious placental inflammatory lesions, particularly those involving the fetal inflammatory response, are significantly correlated with adverse neonatal outcomes. FIR/funisitis was consistently associated with a two-fold increased risk of early-onset neonatal sepsis and elevated risks of prolonged respiratory support and severe intraventricular hemorrhage. Necrotizing funisitis showed the strongest association with neonatal mortality, highlighting its clinical relevance. By contrast, maternal inflammatory response lesions alone (MIR/HCA without FIR) were weakly associated with morbidity, suggesting that fetal involvement may be the critical determinant of neonatal risk.

Our findings align with prior evidence linking intrauterine infection to systemic fetal inflammation and organ dysfunction [2,4,6]. Mechanistic studies support that cytokine cascades triggered by intra-amniotic infection can cross into the fetal circulation, leading to

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 1769-1775 | ISSN:2251-6727

systemic inflammatory response syndrome (SIRS) in the neonate [15,16]. Elevated levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in cord blood have been observed in cases of FIR and are strongly predictive of neonatal sepsis and morbidity [17].

Comparison with previous reviews suggests that this meta-analysis adds precision by stratifying lesions according to MIR and FIR. Earlier narrative syntheses emphasized chorioamnionitis broadly as a risk factor [18], whereas our data indicate that FIR, and not MIR alone, drives the strongest associations. This distinction is important for clinical interpretation: while HCA may be common in preterm birth, it does not uniformly translate into neonatal sepsis risk unless accompanied by FIR.

Clinical implications are substantial. Incorporating placental pathology into neonatal risk stratification could improve early identification of infants at high risk for EOS or severe morbidity. However, challenges remain, including the time required for histopathological reporting and the variability in pathology practices between institutions [14,19]. Point-of-care or rapid pathology approaches, possibly integrated with molecular diagnostics for pathogens, could bridge this gap.

Limitations of the available evidence include heterogeneity in lesion definitions, inconsistent adjustment for confounders such as gestational age and intrapartum antibiotics, and potential publication bias. Although our funnel plot analysis suggested limited bias, the majority of studies were single-center cohorts with moderate risk of bias. Certainty of evidence ranged from moderate for EOS and mortality to low for IVH and composite morbidity, largely due to imprecision and heterogeneity.

Future research should focus on large, prospective, multicenter studies with standardized pathology protocols and integration of microbiological confirmation (e.g., culture, PCR, immunohistochemistry). Such designs would allow stronger causal inference and may establish placental histopathology as a clinical biomarker for neonatal risk prediction.

In conclusion, this meta-analysis underscores the strong correlation between FIR/funisitis and adverse neonatal outcomes, particularly early-onset sepsis and mortality. Maternal inflammatory lesions alone are less predictive, emphasizing the importance of distinguishing maternal versus fetal inflammatory involvement. Standardized pathology reporting and prospective research are essential to fully translate placental findings into neonatal care pathways.

References

1. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med*. 2000;342(20):1500–7.
2. Redline RW. Placental inflammation. *Semin Neonatol*. 2004;9(4):265–74.
3. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. *BJOG*. 2006;113 Suppl 3:17–42.
4. Kim CJ, Romero R, Chaemsaithong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am J Obstet Gynecol*. 2015;213(4 Suppl):S53–69.
5. Kallapur SG, Presicce P, Rueda CM, Jobe AH, Chougnet CA. Fetal immune response to chorioamnionitis. *Semin Reprod Med*. 2014;32(1):56–67.
6. Yoon BH, Romero R, Yang SH, et al. Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with acute funisitis. *Am J Obstet Gynecol*. 1996;174(5):1433–40.
7. Benirschke K, Burton GJ, Baergen RN. *Pathology of the Human Placenta*. 6th ed. Springer; 2012.
8. Schwartz DA. Viral infection and pregnancy: placental immunopathology and clinical outcomes. *Clin Perinatol*. 2017;44(1):1–27.
9. Roberts DJ, Oliva E. Viral and parasitic placentitis. *Arch Pathol Lab Med*. 2006;130(5):526–36.
10. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam

consensus statement. *Arch Pathol Lab Med*. 2016;140(7):698–713.

11. Lee J, Romero R, Kim JS, et al. Funisitis is associated with adverse neonatal outcome in preterm delivery. *J Pediatr*. 2009;154(5):629–34.
12. Park CW, Yoon BH, Kim SM, et al. The relationship between histologic chorioamnionitis and adverse neonatal outcome in preterm infants. *Obstet Gynecol*. 2009;114(6):1206–14.
13. Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Effect of chorioamnionitis on neonatal outcomes among very-low-birth-weight infants. *Am J Epidemiol*. 2008;168(1):55–62.
14. Khong TY, Mooney EE, et al. The Amsterdam Placental Workshop Group consensus statement. *Arch Pathol Lab Med*. 2016;140(7):698–713.
15. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science*. 2014;345(6198):760–5.
16. Gomez R, Romero R, Ghezzi F, et al. The fetal inflammatory response syndrome. *Am J Obstet Gynecol*. 1998;179(1):194–202.
17. Buhimschi CS, Buhimschi IA, Abdel-Razeq S, et al. Placental inflammatory lesions and elevated interleukin-6 in umbilical cord plasma: association with neonatal sepsis. *Am J Obstet Gynecol*. 2003;188(3):753–9.
18. Lau J, Magee F, Qiu Z, Hameed AB. Chorioamnionitis and adverse neonatal outcomes. *Pediatrics*. 2005;116(1):185–90.
19. Redline RW. Inflammatory responses in the placenta and umbilical cord. *Placenta*. 2018;65:104–10.