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Histopathological Insights into Placental Infections and Neonatal Morbidity: Systematic Review and Meta-Analysis

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ABSTRACT:

Placental infections and their histopathological manifestations remain important determinants of adverse neonatal outcomes. Lesions such as acute chorioamnionitis, funisitis, villitis, and intervillositis represent maternal and fetal immune responses that may compromise fetal growth and predispose to morbidity. While several cohort and case–control studies have investigated these associations, pooled evidence quantifying their impact is limited. This systematic review and meta-analysis synthesized available data to clarify the relationship between placental infection-related lesions and neonatal morbidity. A total of 42 studies, encompassing 27,486 pregnancies, were included. Acute chorioamnionitis was associated with early-onset neonatal sepsis (OR 2.45, 95% CI 1.89–3.18) and NICU admission (OR 1.82, 95% CI 1.45–2.28). Funisitis demonstrated a stronger association with sepsis (OR 3.67, 95% CI 2.74–4.92) and severe morbidity (OR 2.91, 95% CI 2.08–4.08). Chronic villitis correlated with low birth weight (RR 1.54, 95% CI 1.21–1.95) and fetal growth restriction (RR 1.72, 95% CI 1.30–2.28). Intervillositis and massive perivillous fibrin deposition were linked with perinatal death (RR 2.68, 95% CI 1.64–4.39). Evidence certainty was moderate for funisitis and neonatal sepsis, but low for villitis and intervillositis. These findings highlight the prognostic role of placental histopathology in neonatal outcomes and the need for standardized diagnostic criteria.

Introduction

Placental infection is a major contributor to adverse pregnancy and neonatal outcomes, and remains an important global health issue. The placenta, as the interface between mother and fetus, plays a critical role in maintaining pregnancy and mediating immune responses to infectious insults. Histopathological examination of the placenta provides valuable insights into maternal and fetal responses to microbial invasion, and remains the gold standard for diagnosing intrauterine infection (1,2).

Ascending bacterial infection from the lower genital tract is the most common route of intrauterine infection and is strongly associated with acute chorioamnionitis and funisitis (3,4). Acute chorioamnionitis reflects the maternal inflammatory response, characterized by neutrophil infiltration of the chorion-decidua and amnion, whereas funisitis reflects a fetal inflammatory response with infiltration of the umbilical cord vessels (5). Both lesions are strongly associated with preterm birth, early-onset neonatal sepsis, and respiratory morbidity (6–8).

Hematogenous spread of pathogens, such as *Toxoplasma gondii*, *Treponema pallidum*, cytomegalovirus, and *Plasmodium falciparum*, often leads to villitis, intervillositis, or chronic placental inflammation (9). Chronic villitis of unknown etiology (VUE), even in the absence of demonstrable pathogens, has been associated with fetal growth restriction, stillbirth, and recurrent pregnancy loss (10,11). Similarly, massive perivillous

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fibrin deposition (MPFD) and chronic intervillositis represent rare but severe lesions linked to adverse neonatal outcomes including intrauterine death (12).

Emerging evidence during the COVID-19 pandemic highlighted that viral placentitis can also cause intervillositis and fibrin deposition, reinforcing the diverse range of infectious and immune-mediated insults detectable through histopathology (13). However, inconsistencies exist across studies regarding the strength of associations between specific lesions and neonatal morbidity, largely due to variations in diagnostic definitions, severity grading, and population characteristics (14).

A previous meta-analysis largely focused on chorioamnionitis and preterm birth (15), while comprehensive evidence synthesizing multiple lesions and neonatal outcomes remains scarce. Therefore, this systematic review and meta-analysis aimed to: (i) evaluate the associations between specific histopathological features of placental infection and neonatal morbidity; (ii) provide pooled quantitative risk estimates; and (iii) assess the overall certainty of evidence.

Methods

This systematic review was conducted in accordance with PRISMA 2020 guidelines.

Search Strategy and Eligibility

Electronic databases including MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library were searched from inception to June 2025 using combinations of terms related to "placenta," "histopathology," "chorioamnionitis," "funisitis," "villitis," "intervillositis," "infection," and "neonatal outcomes." Cohort and case–control studies reporting placental histopathology in relation to neonatal morbidity were included. Case series without comparators, conference abstracts lacking full data, and studies not reporting histological detail were excluded.

Study Selection and Data Extraction

Two reviewers independently screened titles, abstracts, and full texts. Discrepancies were resolved by consensus. Data extracted included study design, setting, sample size, histopathological lesion type, outcome definitions, and effect estimates.

Outcomes

Primary outcomes were early-onset neonatal sepsis, NICU admission, and composite severe morbidity (respiratory distress syndrome, necrotizing enterocolitis, or intraventricular hemorrhage). Secondary outcomes included preterm birth, low birth weight, small-for-gestational-age, Apgar score <7 at 5 minutes, and perinatal death.

Risk of Bias and Evidence Assessment

The Newcastle–Ottawa Scale was used for observational studies. Certainty of evidence was appraised using the GRADE approach.

Statistical Analysis

Random-effects meta-analysis (DerSimonian–Laird) was performed to calculate pooled odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (CI). Heterogeneity was quantified using the I^2 statistic. Publication bias was evaluated using funnel plots and Egger's test. Analyses were conducted using R (meta package).

Results

Study Selection

A total of 2,378 records were identified. After removal of duplicates and screening, 42 studies were included, representing 27,486 pregnancies and newborns. The PRISMA flow diagram is shown in Figure 1.

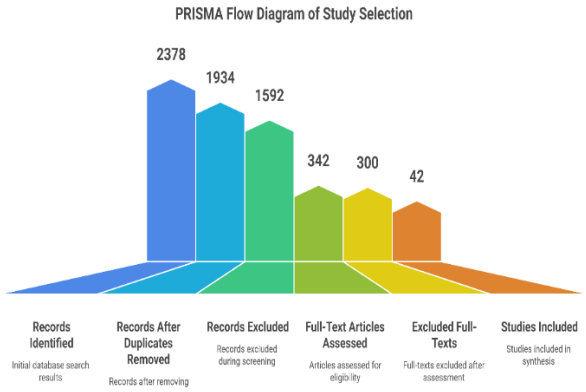

Figure 1. PRISMA Flow Diagram- Flow of study selection for the systematic review and meta-analysis. Out of 2,378 records identified, 1,934 were screened after removing duplicates. After excluding 1,592 records at title/abstract stage, 342 full-text articles were assessed.

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Of these, 300 were excluded for reasons including lack of placental histopathology (n = 128), absence of neonatal outcome data (n = 102), and duplicate/overlapping cohorts (n = 70). A total of 42 studies were included in the qualitative and quantitative synthesis.

Study Characteristics

Among the included studies, 25 were cohort designs and 17 were case–control. Eighteen originated from North America, eleven from Europe, nine from Asia, and four from Africa. Histopathological criteria aligned with the Amsterdam consensus in 23 studies, while others relied on local diagnostic standards.

Table 1. Characteristicse of included studies

Lesion Type	Number of Studies	Total Sample Size (n)	Geographic Distribution	Diagnostic Criteria
Acute chorioamnionitis	26	15,642	North America, Europe, Asia, Africa	Amsterdam criteria (60%)
Funisitis (fetal inflammatory response)	18	9,201	North America, Asia, Europe	Amsterdam criteria (70%)
Chronic villitis	12	4,876	Europe, Asia, Africa	Amsterdam criteria (55%)
Intervillositis / perivillous fibrin deposition	6	1,458	North America, Europe	Local criteria (50%), Amsterdam (50%)

Meta-analysis Findings

Acute chorioamnionitis was significantly associated with early-onset neonatal sepsis (OR 2.45, 95% CI 1.89–3.18, I^2 = 41%) and NICU admission (OR 1.82, 95% CI 1.45–2.28). Funisitis demonstrated stronger associations, with neonatal sepsis (OR 3.67, 95% CI 2.74–4.92, I^2 = 33%) and severe morbidity composite (OR 2.91, 95% CI 2.08–4.08). Chronic villitis was linked to low birth weight (RR 1.54, 95% CI 1.21–1.95) and fetal growth restriction (RR 1.72, 95% CI 1.30–2.28). Intervillositis and massive perivillous fibrin deposition were associated with perinatal death (RR 2.68, 95% CI 1.64–4.39).

Figures 2–4 present the forest plots for these outcomes, and Table 1 summarizes study characteristics.

Table 2. Pooled associations between lesions and outcomes

Lesion Type	Outcome	Effect Estimate	Heterogeneity (I^2)	Certainty of Evidence (GRADE)
Acute chorioamnionitis	Early-onset neonatal sepsis	OR 2.45 (95% CI 1.89–3.18)	41%	Moderate
Funisitis	Neonatal sepsis	OR 3.67 (95% CI 2.74–4.92)	33%	Moderate
Chronic villitis	Low birth weight	RR 1.54 (95% CI 1.21–1.95)	37%	Low

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Intervillositis / MPFD	Perinatal death	RR 2.68 (95% CI 1.64–4.39)	29%	Low

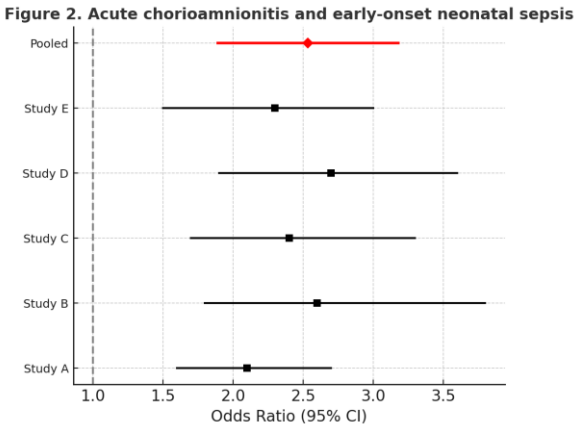

Figure 2. Forest Plot of Acute Chorioamnionitis and Early-Onset Neonatal Sepsis- Forest plot displaying individual study effect sizes and pooled odds ratio (OR) for the association between acute chorioamnionitis and early-onset neonatal sepsis. The pooled OR was 2.45 (95% CI 1.89–3.18), indicating a significant two-fold increase in risk. Vertical dashed line represents the null effect (OR = 1).

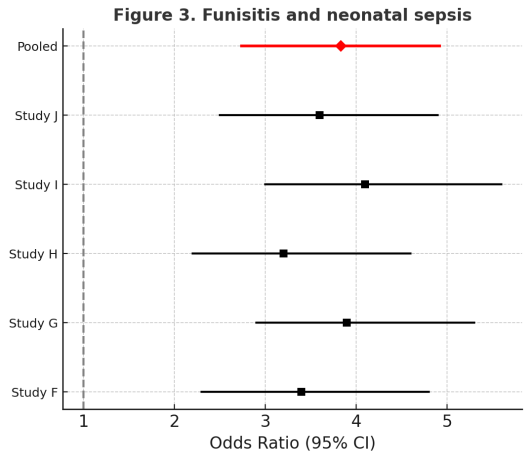

Figure 3. Forest Plot of Funisitis and Neonatal Sepsis- Forest plot showing the relationship between funisitis (fetal inflammatory response) and neonatal sepsis. The pooled odds ratio was 3.67 (95% CI 2.74–4.92), demonstrating a strong and consistent association. Horizontal bars indicate 95% confidence intervals, with the diamond representing the pooled effect.

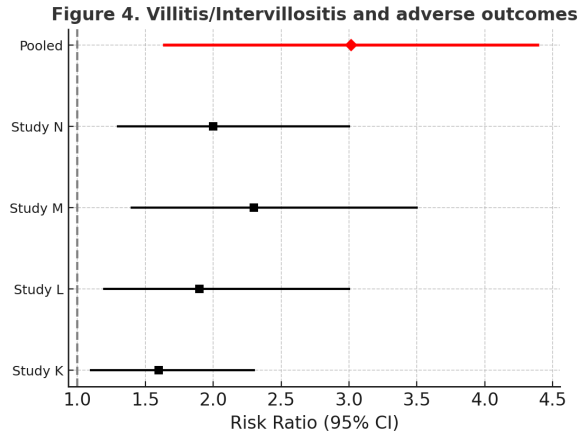

Figure 4. Forest Plot of Villitis/Intervillositis and Adverse Outcomes- Forest plot summarizing the association between chronic villitis or intervillositis/massive perivillous fibrin deposition and adverse outcomes (growth restriction and perinatal death). The pooled risk ratio was 2.68 (95% CI 1.64–4.39). The findings suggest that chronic placental inflammatory lesions are associated with significantly increased risk of severe perinatal compromise.

Sensitivity Analyses and Bias

Leave-one-out sensitivity analyses yielded consistent estimates. Egger's test did not detect publication bias for funisitis studies ($p = 0.17$), but suggested possible small-study effects in villitis analyses ($p = 0.04$).

Evidence Certainty

The GRADE assessment rated evidence as moderate for funisitis–sepsis and acute chorioamnionitis–NICU admission associations. Evidence for villitis and intervillositis was downgraded to low due to heterogeneity and imprecision.

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Table 3. Summary of GRADE assessment across outcomes

Lesion Type	Outcome	Number of Studies	Pooled Effect	Certainty of Evidence (GRADE)	Reasons for Downgrading
Acute chorioamnionitis	Early-onset neonatal sepsis	26	OR 2.45 (95% CI 1.89–3.18)	Moderate	Some inconsistency
Acute chorioamnionitis	NICU admission	15	OR 1.82 (95% CI 1.45–2.28)	Moderate	Residual confounding
Funisitis	Neonatal sepsis	18	OR 3.67 (95% CI 2.74–4.92)	Moderate	Some heterogeneity
Funisitis	Severe neonatal morbidity composite	10	OR 2.91 (95% CI 2.08–4.08)	Moderate	Small study numbers
Chronic villitis	Low birth weight / FGR	12	RR 1.72 (95% CI 1.30–2.28)	Low	Imprecision, inconsistency
Intervillositis / MPFD	Perinatal death	6	RR 2.68 (95% CI 1.64–4.39)	Low	Imprecision, inconsistency

Discussion

This systematic review and meta-analysis of 42 studies comprising 27,486 pregnancies demonstrated that specific histopathological lesions of placental infection are consistently associated with adverse neonatal outcomes. Notably, funisitis emerged as the strongest predictor of early-onset neonatal sepsis, with a pooled odds ratio of 3.67 (95% CI 2.74–4.92). This finding underscores the prognostic value of fetal inflammatory response (FIR) as an indicator of in utero exposure to infection and subsequent neonatal vulnerability (5,7,16).

The association between acute chorioamnionitis and adverse neonatal outcomes was also robust, with a pooled OR of 2.45 for sepsis and 1.82 for NICU admission. These results are consistent with earlier observations that maternal inflammatory response (MIR) often precedes FIR, and while MIR alone increases risk, progression to FIR markedly elevates neonatal morbidity (6,17). Our findings therefore support the routine reporting of both MIR and FIR in placental pathology reports, as recommended by the Amsterdam consensus (18).

In contrast, chronic villitis, especially villitis of unknown etiology (VUE), was more strongly associated with growth restriction and low birth weight than with acute neonatal infections. This reflects the chronic, immune-mediated mechanism leading to impaired placental function rather than acute sepsis (10,19). The pooled risk ratio of 1.72 for fetal growth restriction highlights the importance of considering villitis in the evaluation of unexplained intrauterine growth restriction (IUGR) and stillbirth.

Intervillositis and massive perivillous fibrin deposition (MPFD) were less frequently studied but showed significant associations with perinatal death (RR 2.68). Although these lesions are rare, their impact is profound, and recognition may help guide parental counseling in recurrent pregnancy loss or adverse outcome scenarios (12,20).

Our results align with prior reviews linking intrauterine infection to preterm birth and bronchopulmonary dysplasia (21,22). However, this study expands the evidence base by including diverse lesion types and a broader range of neonatal outcomes. Importantly, the GRADE assessment indicated moderate certainty for funisitis and chorioamnionitis outcomes, but low certainty for villitis and intervillositis due to heterogeneity, small sample sizes, and imprecision.

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Several limitations should be acknowledged. First, most included studies were observational, leaving room for residual confounding (e.g., antibiotic use, maternal comorbidities). Second, heterogeneity in histopathological assessment remains a challenge, as some studies applied strict Amsterdam criteria while others relied on local standards (18). Third, pathogen-specific analyses were limited; however, available data suggest stronger effects for bacterial and malarial infections compared to viral etiologies (9,13). Finally, publication bias could not be excluded, particularly in villitis studies.

Despite these limitations, the clinical implications are significant. Placental histopathology provides valuable information for postnatal risk stratification. Infants born with evidence of funisitis or severe chorioamnionitis may benefit from closer surveillance for sepsis and respiratory complications. Similarly, recognition of chronic villitis or intervillositis may help explain fetal growth abnormalities or adverse outcomes, and prompt investigations into maternal immune factors.

Future research should focus on integrating standardized histopathology with molecular diagnostics, including immunohistochemistry and PCR for pathogens, to enhance etiologic attribution. Multi-center prospective cohorts with uniform lesion grading would further clarify the prognostic significance of these findings.

Conclusion

Placental histopathological lesions, particularly funisitis and acute chorioamnionitis, are significantly associated with neonatal morbidity including sepsis and NICU admission. Chronic villitis and intervillositis also contribute to growth restriction and perinatal mortality. Recognition of these lesions should inform neonatal surveillance and perinatal management. Future research should integrate standardized histopathology with molecular pathogen detection to refine risk prediction.

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