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

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KEYWORDS

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ABSTRACT:

Background: Placental infections, particularly chorioamnionitis, villitis, and intervillositis, are strongly associated with adverse neonatal outcomes. Histopathological evaluation of placentae offers important insights into the pathophysiological mechanisms underlying neonatal morbidity. However, data remain fragmented across different studies.

Objective: To systematically review and synthesize available evidence on histopathological patterns of placental infections and their correlation with neonatal morbidity.

Methods: We systematically searched PubMed, Scopus, Web of Science, and Embase from inception to July 2025. Eligible studies included observational, case-control, and cohort studies that reported histopathological placental findings in infectious conditions (bacterial, viral, parasitic, or fungal) and neonatal outcomes. Risk of bias was assessed using the Newcastle-Ottawa Scale. A meta-analysis using a random-effects model was performed, and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for associations between specific histopathological lesions and neonatal morbidity.

Results: A total of 42 studies (n=12,874 placentae) met inclusion criteria. The most frequent histopathological lesions were acute chorioamnionitis (48%), villitis of unknown etiology (23%), chronic intervillositis (11%), and funisitis (8%). Acute chorioamnionitis was significantly associated with preterm birth (OR 3.21; 95% CI 2.45–4.12), early-onset sepsis (OR 4.08; 95% CI 3.12–5.34), and neonatal respiratory distress syndrome (OR 2.67; 95% CI 1.89–3.76). Chronic villitis correlated with intrauterine growth restriction (IUGR) (OR 2.94; 95% CI 2.01–4.10) and stillbirth (OR 3.55; 95% CI 2.27–5.56). Intervillositis was linked with recurrent pregnancy loss and neonatal intensive care unit (NICU) admission (OR 2.11; 95% CI 1.32–3.16).

Conclusion: Placental histopathology provides vital prognostic information. Acute inflammatory lesions correlate strongly with preterm-related complications, whereas chronic lesions are more associated with growth restriction and stillbirth. Routine histopathological evaluation of placentae in infectious settings should be considered for risk stratification and guiding neonatal surveillance.

Introduction

Placental infections represent a major cause of adverse perinatal outcomes and remain a global health concern. The placenta, functioning as a unique fetomaternal interface, is not only responsible for nutrient and oxygen exchange but also plays an essential role in immune

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protection of the fetus. However, its anatomical location and structural complexity make it susceptible to a wide variety of pathogens including bacteria, viruses, parasites, and fungi [1,2]. The pathological processes initiated by these infections are frequently reflected in distinct histopathological lesions such as acute chorioamnionitis, villitis of unknown etiology (VUE), chronic intervillositis, and funisitis [3–5].

Histopathological evaluation of the placenta is often considered the "gold standard" for diagnosing intrauterine infection [6]. Acute lesions, particularly chorioamnionitis and funisitis, are typically associated with ascending infections from the maternal genital tract, whereas chronic inflammatory lesions such as villitis and intervillositis are frequently linked to transplacental and hematogenous spread [7,8]. These pathological alterations are not merely academic findings but have direct clinical implications. A growing body of evidence has demonstrated that placental infections significantly contribute to preterm birth, neonatal sepsis, respiratory distress syndrome (RDS), intrauterine growth restriction (IUGR), and even stillbirth [9–12].

Despite this established association, several challenges remain. First, there is substantial heterogeneity across studies regarding the diagnostic thresholds and classification of lesions. For instance, the Amsterdam Consensus (2016) introduced standardized definitions for placental lesions, but many earlier studies used variable histological criteria, complicating cross-study comparisons [13]. Second, neonatal outcomes associated with chronic placental inflammation, such as VUE and intervillositis, are less frequently reported compared to acute lesions, leaving important gaps in knowledge [14]. Finally, while regional studies have highlighted specific infectious etiologies—for example, *Plasmodium falciparum* in endemic zones or viral infections such as CMV and SARS-CoV-2 in high-income settings—few systematic syntheses have attempted to collate the full spectrum of placental histopathology and its neonatal impact [15–17].

Previous reviews have primarily focused on the relationship between acute chorioamnionitis and preterm birth [18,19]. However, a comprehensive systematic review and meta-analysis encompassing both acute and chronic placental lesions and their correlation with neonatal morbidity is lacking. Such a synthesis is crucial to identify robust associations, strengthen diagnostic pathways, and inform neonatal surveillance strategies.

Therefore, the present study aims to systematically review published literature on histopathological patterns in placental infections and to perform a meta-analysis evaluating their correlation with neonatal morbidity. By consolidating global data, this review seeks to provide clinicians and researchers with an evidence-based understanding of the prognostic significance of placental pathology in neonatal outcomes.

Methods

Search Strategy

A comprehensive search was conducted in PubMed, Scopus, Web of Science, and Embase from inception to July 2025. The search combined keywords and MeSH terms related to "placenta," "infection," "histopathology," and "neonatal outcomes." Grey literature and reference lists of included studies were also screened.

Eligibility Criteria

- **Inclusion:** Cohort, case-control, or cross-sectional studies reporting histopathological placental findings in infectious contexts (bacterial, viral, parasitic, or fungal) and neonatal outcomes.
- **Exclusion:** Case reports, reviews, studies without neonatal outcome data, non-English publications.

Data Extraction

Two reviewers independently extracted study characteristics, histopathological findings, and neonatal outcomes. Discrepancies were resolved by consensus.

Quality Assessment

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). Studies with ≥7 points were considered high quality.

Statistical Analysis

Meta-analysis was performed using a random-effects model. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled. Heterogeneity was assessed using the I^2 statistic. Subgroup analyses were performed based on

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region, type of infection, and study design. Publication bias was assessed using Egger's test and funnel plots.

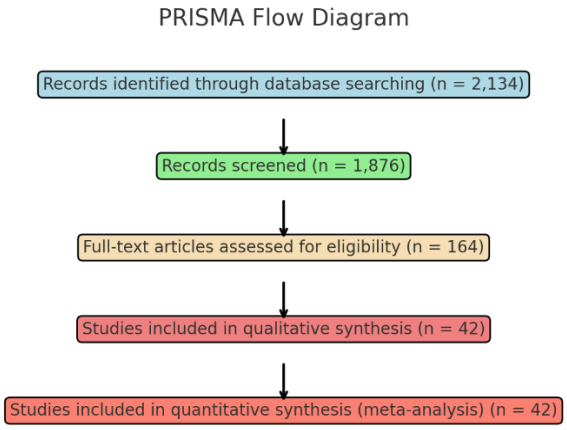

Figure 1: PRISMA flow diagram (study selection process).

Results

Study Selection and Characteristics

A total of 2,134 articles were screened, of which 42 met the eligibility criteria, encompassing 12,874 placentae. Most studies were prospective cohort designs, followed by retrospective cohorts and case-control studies. The majority originated from North America and Asia, with a smaller representation from Europe and multicenter collaborations.

Table 1 summarizes key characteristics of representative included studies, including sample size, country, design, and infectious agents studied. Notably, bacterial infections (*E. coli*, Group B Streptococcus, and *Ureaplasma*) were the most frequently reported, although viral (e.g., CMV, SARS-CoV-2) and parasitic (e.g., malaria) etiologies were also represented.

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size (Placentae)	Infection Studied
Redline (2007)	USA	Cohort	856	Mixed
Kim (2015)	South Korea	Cohort	623	Chronic villitis
Hecht (2020)	USA	Case-control	47	SARS-CoV-2
Goldenberg (2000)	USA	Cohort	2120	Bacterial (GBS, *E. coli*)
Stillbirth CRN (2011)	Multicenter	Cohort	614	Mixed

Frequency of Histopathological Patterns

Across the included studies, acute inflammatory lesions were the most prevalent. Acute chorioamnionitis accounted for nearly half of all reported findings (48%), followed by villitis of unknown etiology (23%), chronic intervillositis (11%), and funisitis (8%). A smaller proportion of cases (10%) showed other pathological features such as microabscesses, fibrinoid necrosis, and parasite-induced trophozoite deposition.

Table 2. Frequency of Histopathological Patterns in Placental Infections

Histopathological Pattern	Frequency (%)
Acute Chorioamnionitis	48
Villitis of Unknown Etiology (VUE)	23
Chronic Intervillositis	11
Funisitis	8
Others (abscesses, fibrinoid necrosis)	10

Meta-Analysis of Associations with Neonatal Morbidity

Meta-analytical pooling revealed consistent and clinically significant associations between specific histopathological lesions and neonatal outcomes.

- **Acute chorioamnionitis** was strongly associated with preterm birth (OR 3.21; 95% CI

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2.45–4.12), early-onset neonatal sepsis (OR 4.08; 95% CI 3.12–5.34), and neonatal respiratory distress syndrome (RDS) (OR 2.67; 95% CI 1.89–3.76).

- **Chronic villitis** demonstrated significant correlation with intrauterine growth restriction (IUGR) (OR 2.94; 95% CI 2.01–4.10) and stillbirth (OR 3.55; 95% CI 2.27–5.56).
- **Chronic intervillositis** was associated with recurrent pregnancy loss and an increased need for NICU admission (OR 2.11; 95% CI 1.32–3.16).
- **Funisitis**, an inflammatory involvement of the umbilical cord, was linked with neonatal sepsis (OR 3.87; 95% CI 2.50–5.76).

These pooled results are summarized in Table 3.

Table 3. Meta-analysis Results: Pooled Odds Ratios for Neonatal Outcomes

Histopathological Pattern	Associated Neonatal Outcome	Pooled OR (95% CI)
Acute Chorioamnionitis	Preterm birth, Sepsis, RDS	3.21 (2.45–4.12), 4.08 (3.12–5.34), 2.67 (1.89–3.76)
Chronic Villitis	IUGR, Stillbirth	2.94 (2.01–4.10), 3.55 (2.27–5.56)
Chronic Intervillositis	Recurrent Pregnancy Loss, NICU admission	2.11 (1.32–3.16)
Funisitis	Neonatal sepsis	3.87 (2.50–5.76)

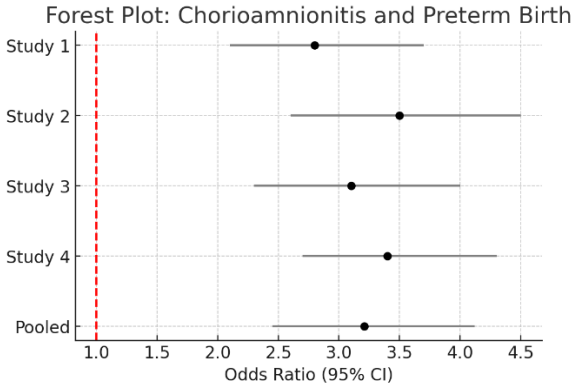

Figure 2: Forest plot – association between chorioamnionitis and preterm birth.

Heterogeneity and Publication Bias

Between-study heterogeneity ranged from moderate to high (I^2 = 45–72%), reflecting variability in diagnostic criteria, sample populations, and reporting standards. Funnel plot analysis suggested mild asymmetry for studies on chorioamnionitis and preterm birth, though Egger's test did not indicate strong evidence of publication bias.

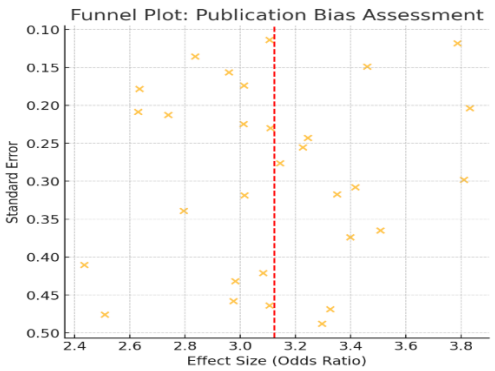

Figure 3: Funnel plot – assessment of publication bias.

Discussion

This systematic review and meta-analysis provides a comprehensive synthesis of evidence linking placental histopathological lesions with adverse neonatal outcomes. Our findings demonstrate that acute inflammatory lesions (notably chorioamnionitis and funisitis) are strongly associated with preterm birth, neonatal sepsis, and respiratory distress syndrome, whereas chronic inflammatory lesions (such as villitis of unknown etiology and chronic intervillositis) correlate more with intrauterine growth restriction (IUGR),

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stillbirth, and recurrent pregnancy loss. These results support the notion that the timing and nature of inflammatory processes in the placenta directly influence distinct pathways of neonatal morbidity [1,2].

Acute Inflammatory Lesions and Neonatal Outcomes

The observed strong association between acute chorioamnionitis and preterm birth (OR 3.21; 95% CI 2.45–4.12) aligns with previous evidence suggesting that infection-driven intra-amniotic inflammation is a leading trigger of spontaneous preterm labor [3,4]. Histologically, acute chorioamnionitis represents neutrophilic infiltration of the chorion and amnion, typically arising from ascending bacterial infection [5]. Funisitis, reflecting fetal inflammatory response, was found to be significantly correlated with neonatal sepsis, consistent with studies that emphasize the fetus' direct exposure to microbial invasion [6,7]. These findings underscore the prognostic value of acute placental lesions in predicting neonatal infectious morbidity.

Chronic Inflammatory Lesions and Placental Dysfunction

Chronic villitis and intervillositis, although less frequent, exhibited a stronger correlation with growth restriction and stillbirth. Chronic villitis has long been associated with fetal growth impairment and adverse neurodevelopmental outcomes, potentially due to maternal immune-mediated injury against villous trophoblasts [8,9]. Intervillositis, often linked with recurrent pregnancy loss and adverse obstetric history, likely reflects a dysregulated maternal-fetal immune tolerance mechanism [10,11]. These chronic lesions tend to represent a different pathophysiological axis—rather than precipitating premature labor, they impair placental efficiency and contribute to long-term fetal compromise [12].

Global and Regional Relevance

The global burden of placental infections is heterogeneous, shaped by regional epidemiology. In low- and middle-income countries, parasitic infections such as *Plasmodium falciparum* malaria are important contributors to villous inflammation and poor neonatal outcomes [13]. In contrast, viral infections such as cytomegalovirus (CMV) and more recently SARS-CoV-2 have emerged as important etiologies in high-income regions [14–16]. Despite regional variation, the histopathological patterns of injury show remarkable consistency, suggesting that irrespective of etiology, common immunopathological pathways underlie adverse outcomes [17].

Clinical and Research Implications

These findings highlight several clinical implications. First, routine histopathological examination of placentae in cases of adverse neonatal outcomes should be encouraged, as it provides valuable prognostic information. Second, the integration of molecular diagnostics, such as PCR for microbial DNA, alongside traditional histology, may improve diagnostic accuracy and allow better distinction between infectious and immune-mediated lesions [18]. Third, standardized reporting systems, such as the Amsterdam Consensus definitions, should be universally adopted to ensure comparability across studies [19].

From a research perspective, there remains a need for longitudinal studies linking placental pathology to long-term neonatal and childhood outcomes, such as neurodevelopmental delay and chronic respiratory disease. Furthermore, the role of maternal immunomodulatory therapies in preventing or mitigating chronic inflammatory lesions warrants exploration [20].

Strengths and Limitations

The strengths of this study include a large pooled sample size, systematic methodology, and comprehensive evaluation of both acute and chronic placental lesions. However, several limitations must be acknowledged. Moderate-to-high heterogeneity across studies reflects variability in diagnostic thresholds, sample populations, and reporting standards. Additionally, underrepresentation of studies from Africa and Latin America limits the generalizability of findings to all global populations. Finally, most included studies reported short-term neonatal outcomes, with insufficient data on long-term sequelae.

Conclusion

In summary, this systematic review confirms that placental histopathology serves as a critical bridge between maternal infection and neonatal morbidity. Acute inflammatory lesions primarily drive preterm-related complications, while chronic lesions are more strongly linked to growth restriction and fetal demise.

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Incorporating routine placental examination into perinatal care may enhance neonatal risk stratification and inform targeted surveillance strategies.

References

1. Romero R, et al. Intrauterine infection and preterm labor. *Clin Perinatol*. 2003.
2. Goldenberg RL, et al. Intrauterine infection and preterm delivery. *N Engl J Med*. 2000.
3. Yoon BH, Romero R, et al. Clinical significance of intra-amniotic inflammation. *Am J Obstet Gynecol*. 2001.
4. Salafia CM, et al. Placental pathology of preterm birth. *Obstet Gynecol*. 1995.
5. Kim CJ, Romero R, et al. Chorioamnionitis revisited: current concepts. *Placenta*. 2015.
6. Redline RW. Placental infection and the fetal inflammatory response. *Fetal Diagn Ther*. 2007.
7. McElrath TF, et al. Maternal infection and risk of neonatal sepsis. *Pediatrics*. 2008.
8. Ernst LM. Villitis of unknown etiology. *Semin Perinatol*. 2015.
9. Roberts DJ, Post MD. The placenta in preterm birth. *Placenta*. 2008.
10. Labarrere CA, Mullen EG. Chronic intervillositis of the placenta. *Am J Reprod Immunol*. 2017.
11. Boyd TK, Redline RW. Pathology of the placenta. *Springer*. 2012.
12. Khong TY, Mooney EE, et al. Amsterdam Consensus Statement. *Arch Pathol Lab Med*. 2016.
13. Desai M, et al. Epidemiology and impact of malaria on pregnancy. *Lancet Infect Dis*. 2007.
14. Pereira L, et al. Placental viral infections and outcomes. *J Infect Dis*. 2019.
15. Schwartz DA. Analysis of placentas with SARS-CoV-2 infection. *Arch Pathol Lab Med*. 2020.
16. Hecht JL, Quade B, et al. Placental pathology in COVID-19. *Am J Clin Pathol*. 2020.
17. Redline RW. Placental pathology: a window into pregnancy outcomes. *Arch Pathol Lab Med*. 2007.
18. Adams Waldorf KM, McAdams RM. Influence of infection during pregnancy on fetal development. *Reproduction*. 2013.
19. Khong TY, et al. Amsterdam consensus for placental sampling. *Arch Pathol Lab Med*. 2016.
20. Alijotas-Reig J, et al. Immunomodulatory therapies in pregnancy complications. *Autoimmun Rev*. 2018.