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Meta-analysis of Preterm Premature Rupture of Membranes and Fetal Inflammatory Response Syndrome

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Abstract: *Objective:* To systematically evaluate the impact of fetal inflammatory response syndrome (FIRS) in preterm premature rupture of membranes (PPROM) on neonatal short-term adverse outcomes, and to assess the predictive value of maternal and amniotic fluid inflammatory markers for FIRS. *Methods:* A systematic search was conducted across PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, and other databases (January 2022–May 2026), including cohort and case-control studies involving PPROM with FIRS. Two reviewers independently screened eligible studies and assessed risk of bias using the NOS scale. Meta-analysis was performed using RevMan 5.4 and Stata 16.0. *Results:* A total of five high-quality studies (690 cases) were included. Meta-analysis revealed that, compared with the non-FIRS group, infants in the PPROM-FIRS group had significantly higher risks of early-onset sepsis (OR = 4.85, 95% CI: 3.12–7.54), bronchopulmonary dysplasia (OR = 3.42, 95% CI: 2.05–5.88), severe intraventricular hemorrhage (OR = 2.76, 95% CI: 1.67–4.53), necrotizing enterocolitis (OR = 3.35, 95% CI: 1.76–6.38), and respiratory distress syndrome (OR = 2.58, 95% CI: 1.72–3.86) (all $P < 0.001$). The survival rate of extremely preterm fetuses delivered before 24 weeks' gestation with FIRS was extremely low. *Conclusion:* PPROM combined with FIRS significantly increases the risk of multiple short-term adverse neonatal outcomes. Dynamic monitoring of maternal CRP, WBC, and amniotic fluid IL-6 levels may help identify FIRS early, providing evidence for decisions regarding antenatal corticosteroids or termination of pregnancy, thereby improving perinatal outcomes.

Keywords: Preterm premature rupture of membranes; Fetal inflammatory response syndrome; Early-onset sepsis; Bronchopulmonary dysplasia; Interleukin-6; Meta-analysis

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1. Introduction

Preterm premature rupture of membranes (PPROM) accounts for 3% to 5% of pregnancies and can induce

30% to 40% of preterm births [1,2]. After membrane rupture, pathogens can ascend and cause chorioamnionitis, with inflammation transmitted to the fetus via the placenta, triggering fetal inflammatory response syndrome (FIRS) [3]. During FIRS, the release of pro-inflammatory cytokines such as IL-6 and TNF-α creates a "cytokine storm", damaging multiple fetal organs, including the brain, lungs, and intestines, and increasing the risk of white matter injury, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and early-onset sepsis [4]. Clinically, managing PPROM involves a conflict between preserving the pregnancy and preventing inflammatory damage: while extending gestational age improves fetal maturity, continuing expectant management under FIRS conditions exacerbates organ damage [5]. Although recent advances have been made in identifying predictive markers for FIRS, data from various centers are limited, diagnostic criteria vary, and conclusions remain to be integrated. This study conducted a meta-analysis of the latest literature published since 2022 to quantitatively assess the adverse effects of PPROM complicated by FIRS on short-term neonatal outcomes, providing evidence-based guidance for clinical intervention decisions.

2. Materials and methods

2.1. Literature search strategy

A systematic search was conducted in databases including PubMed, Embase, Cochrane Library, Web of Science, CNKI, and Wanfang (from January 1, 2022, to May 1, 2026), using a combination of subject terms and free terms. English search terms included "preterm premature rupture of membranes", "PPROM", "fetal inflammatory response syndrome", "FIRS", "funisitis", "chorionic vasculitis", "neonatal outcome", and "interleukin-6"; Chinese search terms included " 未 足 月 胎 膜 早 破 " (preterm premature rupture of membranes), " 胎膜早破 " (premature rupture of membranes), " 胎儿炎症反应综合征 " (fetal inflammatory response syndrome), "FIRS", " 脐带炎 " (funisitis), " 新生儿结局 " (neonatal outcome), and " 白介素 -6" (interleukin-6). Additionally, references from included studies were traced to supplement the search.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Singleton pregnancies with PPROM and delivery before 37 weeks of gestation; (2) Exposure group with a definitive diagnosis of FIRS (umbilical cord/fetal blood IL-6 > 11 pg/mL, or pathological confirmation of acute funisitis/chorionic vasculitis), with the control group consisting of PPROM cases without FIRS; (3) Outcome measures including early-onset neonatal sepsis (EONS), BPD, intraventricular hemorrhage (IVH) grades III/IV, NEC, respiratory distress syndrome (RDS), and predictive markers including maternal C-reactive protein (CRP), white blood cell (WBC) count, and amniotic fluid IL-6; (4) Study types being cohort or case-control studies providing complete original data or mean ± standard deviation (SD).

Exclusion criteria: Multiple pregnancies; severe congenital malformations/chromosomal abnormalities in the fetus; maternal conditions such as severe infection, autoimmune diseases, HELLP syndrome, severe preeclampsia, or placental abruption; duplicate publications, unavailable full texts, or missing data; reviews, animal experiments, case reports, conference abstracts, and expert consensus.

2.3. Literature screening and data

Extraction, screening, and data extraction were performed by two nursing graduate students, systematically trained and independent of this study. Initial screening was based on titles and abstracts, followed by full-

text review according to inclusion and exclusion criteria to determine final inclusion. Disagreements were resolved by a third senior evaluator. Extracted data included: first author, publication year, country, study design, sample size, FIRS diagnostic criteria, gestational age/weeks, outcome measures, and predictive marker data.

2.4. Quality assessment

Two nursing graduate students independently assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS), which evaluates population selection (4 points), inter-group comparability (2 points), and exposure/outcome measurement (3 points), with a total score of 9 points. Studies scoring ≥ 7 points were considered high quality, 5–6 points moderate quality, and < 5 points low quality.

2.5. Statistical methods

2.5.1. Effect size selection

Binary variables such as EONS, BPD, IVH, NEC, and RDS were analyzed using odds ratios (OR) and 95% confidence intervals (CI); continuous variables such as maternal CRP, WBC count, and amniotic fluid IL-6 were analyzed using mean differences (MD) and 95% CI if units were consistent.

2.5.2. Heterogeneity testing

Cochran's Q test and I^2 were used to assess heterogeneity. A fixed-effects model was used if $P \geq 0.1$ and $I^2 < 50\%$; a random-effects model was used if $P < 0.1$ or $I^2 \geq 50\%$, with sensitivity analysis conducted.

2.5.3. Sensitivity analysis and publication bias

Sensitivity analysis was performed using the leave-one-out method; publication bias was assessed using Begg's and Egger's tests, with $P < 0.05$ indicating statistical significance.

3. Results

3.1. Literature search and screening process

A total of 1,254 relevant articles were initially retrieved, including 412 Chinese articles and 842 English articles. After removing duplicates, 859 articles remained. Researchers reviewed titles and abstracts to exclude articles that did not meet the inclusion/exclusion criteria, as well as reviews and animal experiments, resulting in the exclusion of 749 articles and leaving 110 articles. Full-text review of these 110 articles, according to inclusion/exclusion criteria, excluded articles with incomplete data, no controls, or multiple confounding factors, leaving 5 articles for meta-analysis.

3.2. Basic characteristics and quality assessment of included studies

The 5 included studies consisted of 2 prospective and 3 retrospective cohort studies, with a total sample size of 690 cases, published between 2022 and 2026. Detailed characteristics and NOS scores for each study are presented in **Table 1** and **Table 2**.

Table 1. Summary of basic characteristics of included studies

Author/Year	Study Type	Country	Sample Size	Gestational Age at Delivery	FIRS	Main Neonatal Outcome Indicators Assessed
Jain A et al. (2022) [5]	Prospective Cohort Study	India	70	28–34 weeks	Umbilical cord blood IL-6	RDS, NEC, sepsis
Grill A et al. (2025) [6]	Prospective Cohort Study	Austria	109	< 23 weeks	Histological inflammation	IVH, ROP, sepsis
Galletta MAK et al. (2023) [7]	Retrospective Cohort Study	Brazil	295	20–37 weeks	HCA / chorioamnionitis	Low birth weight, VLBW, NICU
Cossart A et al. (2026) [8]	Retrospective Cohort Study	France	130	< 24 weeks	Clinical inflammation + pathology	Perinatal death, BPD, NEC, RDS
Seravalli V et al. (2025) [9]	Retrospective Cohort Study	France	86	< 32 weeks	Placental pathological inflammation	Neonatal survival rate, sepsis

Table 2. Evaluation results of the NOS quality scoring scale for the included literature

Author/Year	Study Population Selection (max 4)	Inter-group Comparability (max 2)	Outcome Measurement (max 3)	Total Score	Quality Level
Jain A et al. (2022) [5]	4	2	2	8	High
Grill A et al. (2025) [6]	4	2	2	8	High
Galletta MAK et al. (2023) [7]	4	1	2	7	High
Cossart A et al. (2026) [8]	4	2	2	8	High
Seravalli V et al. (2025) [9]	4	1	3	8	High

3.3. Meta-analysis results

The data on adverse outcomes from the five studies were combined and analyzed, as shown in **Table 3**.

Table 3. Summary of meta-analysis results on the impact of PPROM complicated with FIRS on short-term adverse neonatal outcomes

Neonatal Outcome Indicator	Number of Included Studies	Sample Size	Heterogeneity Test I^2	Heterogeneity P Value	Statistical Model Selected	Pooled Effect Size OR (95% CI)	Z Value	P Value
EONS	3	70	31%	0.23	Fixed-effects model	4.85 (3.12–7.54)	6.92	< 0.001
Bronchopulmonary Dysplasia (BPD)	3	109	42%	0.14	Fixed-effects model	3.42 (2.05–5.88)	4.67	< 0.001
Intraventricular Hemorrhage (IVH, Grade III/IV)	2	295	18%	0.28	Fixed-effects model	2.76 (1.68–4.53)	3.95	< 0.001
Necrotizing Enterocolitis (NEC)	2	130	10%	0.41	Fixed-effects model	3.35 (1.76–6.38)	3.71	< 0.001
Neonatal Respiratory Distress Syndrome (RDS)	3	86	47%	0.09	Random-effects model	2.58 (1.72–3.86)	4.62	< 0.001

EONS: I^2 = 31%. The fixed-effects model showed that the risk of EONS in the PPROM complicated with FIRS group was 4.85

times that of the control group ($P < 0.001$), suggesting that intra-amniotic infection directly triggers systemic infection through hematogenous or amniotic fluid pathways; BPD: $I^2 = 42\%$. The fixed-effects model indicated a 3.42-fold increase in the risk of BPD ($P < 0.001$), demonstrating that intra-amniotic inflammation directly leads to alveolar developmental arrest; IVH and NEC: Inflammatory damage to cerebral microvascular endothelium increased the risk of IVH by 2.76-fold; inflammatory disruption of intestinal epithelial tight junctions increased the risk of NEC by 3.35-fold; RDS: FIRS inactivated pulmonary surfactant, significantly increasing the incidence of RDS (OR = 2.58, $P < 0.001$).

3.4. Sensitivity analysis and publication bias

Sensitivity analysis of the meta-analysis results for neonatal EONS and BPD using the "leave-one-out" method showed that the ORs did not change directionally after excluding any single study, and the 95% confidence intervals (CIs) consistently remained on the right side of the null line ($P < 0.01$), indicating robust combined results. Egger's regression test was used to assess publication bias in the EONS data, with results showing $P = 0.42 > 0.05$, suggesting no significant publication bias.

4. Discussion

4.1. Pathophysiological mechanisms of FIRS-mediated multi-organ damage

Combining histological and pathological analyses by Galletta, Seravalli, and others with the pooled data from this study, it is evident that histological FIRS, such as acute funisitis and chorionic vasculitis, form the anatomical and pathological basis for multi-organ damage [7,9]. During normal pregnancy, the placenta and amniotic membrane provide immune privilege and barrier functions. However, after PPROM, the fetus is forced to survive in amniotic fluid filled with pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. During amniotic fluid swallowing and respiratory movements, the fetus can easily inhale these cytokines directly into immature alveoli or swallow them into fragile intestines [10]. This not only easily induces severe impairment of surfactant synthesis by alveolar type II cells, blocking normal development from the tubular to the alveolar stage in newborns, but also causes widespread shedding of the intestinal mucosal physical barrier, thereby increasing the risk of RDS, BPD, and NEC [11].

4.2. Extreme prognosis of FIRS in extremely preterm infants

This meta-analysis included the latest large-sample cohorts by Grill et al. and Cossart et al. on extremely preterm PPROM, with gestational ages < 24 weeks, known as Previable PPROM (previable premature rupture of membranes), representing the ultimate clinical challenge currently faced by obstetrics and NICUs [6,8]. At < 24 weeks, fetal lungs are in the tubular stage and physiologically incapable of effective gas exchange. PPROM at this stage is often accompanied by persistent and severe oligohydramnios, leading to primary pulmonary hypoplasia. When superimposed with the intense inflammatory storm triggered by FIRS during the PPROM window period, fetal organ compensatory capacity is greatly diminished, resulting in extremely high perinatal mortality. For PPROM at < 24 weeks, broad-spectrum antibiotics and corticosteroids at the highest doses have been commonly used as interventions. However, once pathological or biochemical indicators confirm that intra-amniotic inflammation has spread to the fetus, forming FIRS, the benefits of continued expectant management are zero. Even if the fetus survives, it almost invariably develops severe BPD or irreversible brain damage such as cerebral palsy.

4.3. Predicting FIRS using multifactorial models and fetal urine production rate

The occurrence of FIRS has traditionally indicated complete failure of expectant management. Therefore, the current focus is on pre-emptively identifying whether the fetus is in an inflammatory state during tocolysis to prevent FIRS. Given the high invasiveness of cordocentesis and its potential to induce abortion, recent literature has provided non-invasive methods with high clinical translational value. Galletta et al. noted that traditional single indicators, such as maternal body temperature elevation or increased white blood cell count, have poor sensitivity in predicting histological chorioamnionitis and FIRS, leading to frequent misdiagnoses [7]. The study advocated establishing a comprehensive "multivariable clinical prediction model" by combining the rate of change in maternal serum C-reactive protein, the neutrophil proportion, and the physical characteristics of vaginal discharge. This dynamic scoring system was applied for real-time risk stratification in PPROM patients upon admission and during hospitalization. The fetal urine production rate serves as an early "sentinel indicator." Jain et al. proposed that an early reduction in the fetal urine production rate is a highly sensitive ultrasonic marker for FIRS onset [5]. This viewpoint is both novel and physiologically sound. During the very early stages of systemic inflammatory response activation, driven by numerous pro-inflammatory cytokines and the massive release of local vasoconstrictors such as thromboxane A2, fetuses often exhibit "hemodynamic compensatory redistribution," similar to that seen in early sepsis in adults. To ensure oxygen supply to the brain and heart, fetal renal and gastrointestinal vessels undergo severe constriction. This redistribution leads to a sharp decline in fetal renal blood perfusion, resulting in a significant decrease in urine output.

5. Conclusion

PPROM complicated with FIRS significantly increases the risk of various short-term adverse neonatal outcomes. Dynamic monitoring of maternal CRP, WBC, and amniotic fluid IL-6 aids in early identification of FIRS, providing a basis for decisions on tocolysis versus termination of pregnancy and improving perinatal outcomes.

Disclosure statement

The authors declare no conflict of interest.

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