

Research on the Correlation between Amniotic Microecological Changes and Intrauterine Inflammatory Response Following Preterm Premature Rupture of Membranes

Wenqi Zhou, Liping Zhu, Ke Huang, Lu Bai, Qin Yang*

Department of Neonatology, The Affiliated Changsha Central Hospital, Hengyang Medical School, University of South China, Changsha, China

Email: *995798884@qq.com

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Abstract

Objective: To investigate the effect of preterm premature rupture of membranes (PPROM) on the amniotic fluid microbiome and analyze its correlation with intrauterine inflammatory responses. **Methods:** A total of 30 preterm infants born at Changsha Central Hospital and admitted to the Neonatal Department between January 2023 and June 2025 were enrolled, including 10 without PPROM and 20 with PPROM. Metagenomic sequencing was performed to analyze changes in the amniotic fluid microbiome. Placental and umbilical cord pathology, as well as inflammatory markers of the preterm infants, were also collected. **Results:** In the non-PPROM group, genes of bacteria, fungi, and viruses were detectable in the amniotic fluid, with bacteria being predominant. *Cutibacterium acnes*, *Staphylococcus epidermidis*, and *Staphylococcus hominis* were the most common bacterial species, while *Lasiodiplodia*, *Aspergillus*, and Human endogenous retrovirus K were the most frequently detected fungi and virus, respectively, although their copy numbers were low. *Ureaplasma* was detected in 8 cases in the PPROM group. Compared with the non-PPROM group, bacterial and fungal copy numbers were significantly higher in the PPROM group ($P < 0.05$). Placental/umbilical cord pathology showed inflammatory changes in 8 cases, all of which occurred in the PPROM group. No significant difference in the amniotic fluid microbiome was observed between PPROM cases with normal placental/umbilical cord pathology and those with inflammatory changes ($P > 0.05$). **Conclusion:** A unique microecological environment exists in amniotic fluid. The occurrence

of PPRM is associated with alterations in the composition of the amniotic fluid microbiome, which may be related to the development of intrauterine inflammatory responses.

Keywords

Preterm Prelabor Rupture of Membranes (PPROM), Preterm Infant, Amniotic Fluid, Microecosystem, Intrauterine Inflammation

1. Introduction

As the incidence of preterm birth continues to rise each year, the management of preterm infants has become an increasingly important research focus in perinatal medicine. Preterm premature rupture of membranes (PPROM) is one of the leading causes of preterm birth. PPRM is often closely associated with intrauterine infection: occult intrauterine infections can trigger PPRM, while prolonged PPRM facilitates easier and faster retrograde pathogen invasion. The severity of infection correlates with the duration of PPRM [1] [2]. Fetal exposure to pathogens such as bacteria, viruses, and fungi in utero can induce an inflammatory response known as fetal inflammatory response syndrome (FIRS). FIRS resembles adult systemic inflammatory response syndrome (SIRS) and may lead to multi-system involvement in the fetus or neonate. It can initiate labor, increase neonatal morbidity, and cause multi-organ dysfunction. Both mother and fetus produce pro-inflammatory cytokines in response to intra-amniotic infection, resulting in a high risk of adverse outcomes—particularly preterm birth, early-onset sepsis, bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, neonatal respiratory distress syndrome, and even death [3]-[5].

In utero, the fetus may already be exposed to bacteria in the amniotic fluid, with both fetus and mother encountering microorganisms and their metabolites. When PPRM occurs, it remains unclear whether and how the composition of the intrauterine microbiota changes, and which specific alterations are linked to the onset and progression of FIRS. We hypothesize that PPRM leads to dysbiosis of the intrauterine microbiome, and that these changes are closely associated with intrauterine inflammation and directly influence the prognosis of preterm infants. This study aims to use metagenomic detection to identify early abnormal shifts in the intrauterine microbiota and to screen for specific pathogens. Such an approach would be valuable for clarifying the mechanisms of intrauterine inflammation, predicting its occurrence, and improving the diagnosis, treatment, and outcomes of preterm infants.

2. Materials and Methods

2.1. Study Population

Preterm infants delivered at Changsha Central Hospital and subsequently admit-

ted to the Department of Neonatology between January 2023 and December 2025 were enrolled.

1) Inclusion criteria for the PPRM group:

Infants born at <37 weeks of gestation who met the diagnostic criteria for preterm premature rupture of membranes (PPROM), were delivered at our hospital's obstetrics department, had a duration of membrane rupture of less than 7 days, and whose guardians provided written informed consent.

2) Inclusion criteria for the control group:

Preterm infants born at <37 weeks of gestation without PPRM, delivered at our hospital, with no high-risk factors or clinical signs of intrauterine infection and no evidence of fetal inflammatory response syndrome (FIRS), and whose guardians provided written informed consent.

3) Exclusion criteria:

Infants with a gestational age ≥ 37 weeks, those not born at our hospital, or those whose guardians declined to participate in the study.

This study was approved by the Medical Ethics Committee of Changsha Central Hospital (Approval No. 2022-202).

2.2. Specimen Collection and Testing

A standardized clinical data collection form was designed. Designated personnel collected relevant information for each group, including neonatal sex, gestational age, birth weight, mode of delivery, diagnosis, feeding method, complications, and maternal pregnancy history. At birth, amniotic fluid and meconium samples were collected from preterm infants for metagenomic analysis. Metagenomic sequencing (performed by Hunan Jieyi Health Medical Laboratory Co., Ltd.) was used to characterize the bacterial microbiota in the amniotic fluid specimens. Umbilical cord and placental samples were collected, fixed in formalin, processed into paraffin sections, and stained with hematoxylin and eosin (HE). Umbilical cord blood was also obtained to measure complete blood count, C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6).

All amniotic fluid samples were collected during cesarean section, immediately after rupture of membranes, by obstetricians using strict aseptic technique via puncture. Sample collection was completed before the mother received any intrapartum antibiotic treatment to minimize the risk of iatrogenic contamination. After collection, samples were immediately aliquoted into sterile cryovials and stored at -80°C until testing.

Metagenomic sequencing was performed by Hunan Jieyi Health Medical Laboratory Co., Ltd. Total DNA was extracted from amniotic fluid samples using the QIAamp DNA Mini Kit (Qiagen, Germany). Sequencing was conducted on the Illumina NovaSeq 6000 platform with 150 bp paired-end reads (PE150). After quality control filtering to remove adapters and low-quality reads ($Q < 20$), species annotation was performed using Kraken2 software (reference database: NCBI RefSeq complete genome library, version 2023). Species classification criteria were

defined as follows: at the genus level, reads ≥ 2 and relative abundance $\geq 0.1\%$; at the species level, reads ≥ 2 and relative abundance $\geq 0.01\%$. “Copy number” was defined as the number of unique reads aligned to a specific species genome after normalization by sequencing depth. No-template controls (NTC) were included during both DNA extraction and library preparation. Sequencing results showed that the NTC contained only minimal background signals and did not form any dominant bacterial species. Potential contaminants in the samples were identified and evaluated using the decontam R package (prevalence method).

2.3. Statistical Analysis

Statistical analyses were performed using SPSS version 27.0. Normally distributed data with homogeneous variance were expressed as mean $\pm$ standard deviation and compared between groups using the independent-samples t-test. Data that were not normally distributed or had unequal variances were expressed as median and range [M (minimum, maximum)] and compared using the Mann-Whitney U test. Categorical variables were compared using Fisher’s exact test. All tests were two-sided, and a P-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

A total of 30 cases met the inclusion and exclusion criteria and were enrolled in the study, including 10 cases in the non-PPROM group and 20 cases in the PPROM group. There were no significant differences between the two groups in gestational age, birth weight, umbilical cord blood white blood cell count (WBC), neutrophil percentage (N%), platelet count (PLT), C-reactive protein (CRP), or procalcitonin (PCT) ($P > 0.05$). All mothers in the PPROM group received prenatal antibiotics, whereas none in the non-PPROM group did. Bacterial cultures of blood and amniotic fluid were negative in all cases. Placental and umbilical cord pathology showed no abnormalities in the non-PPROM group. In the PPROM group, 5 cases had isolated chorioamnionitis and 3 cases had fetal inflammatory response; the difference between the two groups was statistically significant. There were no significant differences between the groups in the duration of early antibiotic use or mortality ($P > 0.05$). Details are shown in **Table 1**.

Table 1. Comparison of baseline characteristics between the non-PPROM group and the PPROM group ($x \pm s$).

	Non-PPROM group (n = 10)	PPROM group (n = 20)	t value	P value
Gestational age at birth (weeks)	35.56 $\pm$ 0.82	35.18 $\pm$ 0.83	1.410	0.246
Birth weight (g)	2388.0 $\pm$ 249.5	2454.3 $\pm$ 276.6	0.407	0.529
WBC ($\times 10^9/L$)	10.31 $\pm$ 3.07	12.26 $\pm$ 2.81	3.004	0.094
N (%)	51.32 $\pm$ 12.74	56.97 $\pm$ 9.87	1.796	0.191

Continued

PLT ($\times 10^{12}/L$)	294.80 $\pm$ 73.44	273.18 $\pm$ 69.98	0.580	0.453
CRP (mg/L)	5.40 $\pm$ 0.52	12.00 $\pm$ 25.50	0.627	0.435
PCT (mg/L)	0.11 $\pm$ 0.12	1.20 $\pm$ 2.55	1.792	0.191
Chorioamnionitis/Fetal inflammatory response (n)	0	8	-	0.029*
Duration of early antibiotic use (days)	4.9 $\pm$ 3.0	6.2 $\pm$ 2.3	1.712	0.203
Number of deaths (n)	0	1	-	1.000*

*: Fisher's exact test.

3.2. Microbiota Distribution Characteristics Detected by Metagenomics in the Non-PPROM Group

In the amniotic fluid of preterm infants in the non-PPROM group, genes from bacteria, fungi, and viruses were detected, with bacteria being the predominant component. Based on analysis of the top five bacterial species ranked by copy number in each amniotic fluid sample, *Cutibacterium acnes* was the most prevalent bacterium among the top five in the non-PPROM group (7/10). *Staphylococcus epidermidis* and *Staphylococcus hominis* were also relatively common (3/10). The remaining 34 bacterial species appeared in the top five in only one or two individuals, indicating strong inter-individual variability.

Cladosporium and *Aspergillus* were the most commonly detected fungal genera in the non-PPROM group, present in 90% of individuals. *Malassezia* and *Lachancea* were also frequently detected, appearing in 80% of individuals. The remaining eight fungal genera were identified in only 1 to 4 individuals. Human endogenous retrovirus K was the most prevalent virus in the non-PPROM group, detected in 60% of individuals. No *Mycoplasma* species were detected in the amniotic fluid of the non-PPROM group.

3.3. Comparison of Microbiota Distribution Detected by Metagenomics between the Non-PPROM and PPRM Groups

There were no significant differences between the non-PPROM and PPRM groups in the number of bacterial species, the proportion of Gram-negative bacteria, the number of fungal species, the number of viral species, or viral copy numbers ($P > 0.05$). However, bacterial and fungal copy numbers were significantly higher in the PPRM group compared with the non-PPROM group ($P < 0.05$). *Ureaplasma* was detected in 8 cases in the PPRM group. Details are shown in Table 2.

3.4. Comparison of Microbiota Distribution Detected by Metagenomics between the Normal Placental/Umbilical Cord Pathology Group and the Placental/Umbilical Cord Inflammation Group

PPROM cases were divided into two subgroups according to the presence or ab-

sence of placental/umbilical cord inflammation: the normal pathology group and the inflammation group. There were no significant differences between the two groups in bacterial copy number, number of bacterial species, proportion of Gram-negative bacteria, *Ureaplasma* copy number, fungal copy number, number of fungal species, number of viral species, or viral copy number ($P > 0.05$). Details are shown in **Table 3**.

Table 2. Comparison of microbiota distribution detected by metagenomics between the non-PPROM group and the PPROM group [M (P25-P75)].

	Non-PPROM group (n = 10)	PPROM group (n = 20)	P value
Bacterial copy number	457.0 (136.8, 1276.5)	1489 (687.8, 4627.3)	0.024
Number of bacterial species	16.5 (7.8, 41.0)	31 (22.3, 50.0)	0.100
Proportion of Gram-negative bacteria (%)	52.94 (23.62, 83.79)	63.4 (25.8, 84.1)	0.373
<i>Ureaplasma</i> copy number	-	0.0 (0.0, 11.5)	-
Number of fungal species	9.0 (7.0, 10.3)	10.5 (7.0, 14.8)	0.248
Fungal copy number	86.5 (78.8, 122.5)	146.0 (82.0, 525.3)	0.044
Number of viral species	1.5 (0.8, 2.0)	1.0 (1.0, 2.0)	0.713
Viral copy number	4.5 (1.5, 7.3)	4.0 (1.5, 7.0)	0.713

Table 3. Comparison of microbiota distribution detected by metagenomics between the normal placental/umbilical cord pathology group and the placental/umbilical cord inflammation group [M (P25-P75)].

	Normal placental/umbilical cord pathology group (n = 12)	Placental/umbilical cord inflammation group (n = 8)	P value
Proportion of Gram-negative bacteria (%)	64.12 (30.34, 76.73)	59.1 (21.3, 89.2)	0.939
Bacterial copy number	1348.0 (726.5, 4251.0)	1861.0 (232.8, 251430.5)	0.887
Number of bacterial species	28.0 (23.0, 49.0)	33.0 (18.0, 71.0)	0.938
<i>Ureaplasma</i> copy number	0.0 (0.0, 134.9)	0.0 (0.0, 1205.5)	0.089
Number of fungal species	11.0 (7.5, 14.8)	10.0 (7.0, 14.5)	0.755
Fungal copy number	145.5 (80.5, 586.8)	125.5 (88.3, 475.8)	0.908
Number of viral species	1.0 (0.3, 1.8)	1.0 (1.0, 2.0)	0.110
Viral copy number	4.0 (0.3, 6.5)	4.5 (3.3, 9.3)	0.368

Due to the limited sample size, we further calculated the effect sizes of the main indicators. The Mann-Whitney U test comparing *Ureaplasma* copy numbers between the normal placental/umbilical cord pathology group and the inflammation group yielded a rank correlation effect size of $r = 0.28$ (95% CI: -0.05 to 0.56), indicating a small effect size with the confidence interval crossing zero. This finding is consistent with the previous inconclusive results.

4. Discussion

It has traditionally been assumed that the blood-placental barrier and fetal membranes protect the amniotic fluid from microbial invasion, allowing the fetus to develop in a sterile environment [6]. However, with advances in detection technologies, recent studies have identified microbial DNA colonizing both amniotic fluid and the placenta. These microorganisms are thought to originate from the birth canal and the maternal gastrointestinal tract. Through fetal breathing and swallowing movements, the fetal respiratory and gastrointestinal tracts are exposed to microorganisms and their components. Related studies have shown that meconium contains viable microorganisms and their DNA, and that the microbial composition of amniotic fluid, meconium, and placenta varies with gestational age. Importantly, these microorganisms do not appear to trigger fetal inflammatory response syndrome (FIRS) [7]-[9].

In this study, among cases without preterm premature rupture of membranes (PPROM) or other evidence of maternal infection, none developed chorioamnionitis. However, metagenomic analysis of the amniotic fluid still revealed the presence of a microbial ecosystem, with detectable gene copies of bacteria, fungi, and viruses. Among the bacteria, *Cutibacterium acnes*, *Staphylococcus epidermidis*, and *Staphylococcus hominis* were the most frequently detected species. The most common fungi and virus were *Lasiodiplodia*, *Aspergillus*, and human endogenous retrovirus K, respectively, although their copy numbers were very low. These findings only indicate that bacterial, fungal, and viral genetic material can be detected in amniotic fluid, which may constitute a unique microbial genetic environment within the amniotic cavity. However, as previous studies have pointed out [7] [9], distinguishing true colonizing microbiota from background contamination or transient microbial DNA remains highly challenging in low-biomass samples. Therefore, whether the microbial DNA detected in this study represents an active, colonizing “normal amniotic fluid microbiota” requires further investigation, and its physiological significance remains to be clarified.

When the fetus is exposed in utero to pathogenic microorganisms such as bacteria, viruses, or fungi, these pathogens must first cross the placenta via the umbilical vessels to enter the fetal circulation, triggering chorioamnionitis [10] [11]. The fetus then mounts an inflammatory response by producing pro-inflammatory cytokines against the intra-amniotic infection, which can induce fetal inflammatory response syndrome (FIRS). The pathophysiological process that initiates FIRS is histologically characterized by umbilical vasculitis. FIRS can trigger the onset of labor, leading to preterm birth. If pregnancy is not terminated, FIRS may cause persistent multi-system damage to the fetus that continues after delivery, markedly increasing the risk of neonatal complications and adverse outcomes [12]-[15].

PPROM may be a consequence of intrauterine infection, or it may induce intrauterine infection due to prolonged membrane rupture. However, PPRM does not necessarily indicate the presence of inflammatory pathology in the placenta

or umbilical cord [16]-[18]. In this study, placental and umbilical cord pathology revealed chorioamnionitis and/or funisitis in fewer than half of the PPRM cases. This suggests that PPRM does not inevitably trigger inflammatory responses in the placenta or fetus. Furthermore, there were no significant differences in inflammatory markers between the PPRM and non-PPRM groups among the preterm infants. Nevertheless, the copy numbers of bacteria and fungi in the amniotic fluid were significantly higher in the PPRM group, indicating that PPRM leads to alterations in the amniotic fluid microbiome, characterized primarily by an increase in bacterial and fungal abundance. This change may be one of the reasons why PPRM is a high-risk factor for neonatal infection. Among the PPRM cases, no significant differences were observed in the composition or quantity of amniotic fluid microorganisms between the subgroups with and without placental/umbilical cord inflammatory changes. However, due to the small sample size in this subgroup analysis, the statistical power was limited. Therefore, this result should be considered inconclusive rather than evidence of no association. For example, the median *Ureaplasma* copy number was higher in the inflammation group, but the difference did not reach statistical significance. Future studies with larger sample sizes are needed to further clarify this relationship.

Currently, when PPRM occurs, antibiotics are routinely administered to both pregnant women and preterm infants [19]-[21]. In the present study, mothers in the PPRM group received prenatal antibiotics, whereas those in the non-PPRM group did not. However, there was no significant difference between the two groups in the duration of early postnatal antibiotic use among preterm infants. Notably, the non-PPRM group showed no evidence of intrauterine inflammation, and PPRM itself does not necessarily lead to intrauterine inflammatory responses. These findings suggest that empirical antibiotic use should be approached with caution in the absence of PPRM and other evidence of intrauterine infection. Even in cases of PPRM, antibiotics should be discontinued promptly once intrauterine bacterial infection has been excluded. Otherwise, unnecessary antibiotic exposure may disrupt the normal intrauterine microbiome, with potential but still unknown consequences for preterm infants.

This study has an important limitation: all mothers in the PPRM group received antenatal antibiotic treatment, whereas those in the control group did not. This represents an unavoidable confounding factor. Therefore, the observed differences in microbial load in the amniotic fluid between the PPRM and control groups may be attributable to PPRM itself, antibiotic exposure, or their combined effects. Antibiotic use may have suppressed the growth of certain susceptible microorganisms, thereby altering the composition and abundance of the microbial community. Accordingly, the conclusions of this study should be interpreted as reflecting an association between PPRM status combined with antibiotic exposure and the microbial findings, rather than being attributed solely to PPRM. Future studies with more refined designs are needed to distinguish the independent effects of PPRM and antibiotics on the amniotic fluid microbiome.

5. Conclusion

In conclusion, a unique microecological environment exists in the amniotic fluid, which may play an important role in fetal growth, development, and maturation. The occurrence of PPROM is associated with changes in the composition of the amniotic fluid microbiome, and these alterations may be related to the development of intrauterine inflammatory responses.

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Author Contributions

Wenqi Zhou performed the ELISA and pathological analyses and contributed to manuscript writing. Liping Zhu and Ke Huang collected the specimens. Lu Bai conducted the metagenomic analysis. Qin Yang provided guidance on manuscript writing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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