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MATERNAL AND FETAL INFLAMMATORY RESPONSE AS A DETERMINANT OF NEONATAL OUTCOMES IN PRETERM BIRTHS: A CLINICOPATHOLOGICAL CASE SERIES OF 30 PLACENTAS

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Abstract
Background: Preterm birth is one of the major causes of neonatal morbidity and mortality worldwide. Intrauterine infection and inflammation are important contributors to spontaneous preterm labour, with chorioamnionitis being a common associated pathology. Placental histopathological examination remains the gold standard for identifying subclinical chorioamnionitis.
Objective: To study the histopathological features of chorioamnionitis in preterm placentas and to correlate maternal inflammatory response (MIR) and fetal inflammatory response (FIR) with neonatal outcome.
Methods: This retrospective case series included 30 placentas from preterm deliveries (<37 weeks gestation) showing histological evidence of chorioamnionitis. Routine hematoxylin and eosin stained sections were examined. Inflammatory changes were classified into maternal and fetal inflammatory responses using standard histopathological criteria. Relevant maternal and neonatal clinical details were obtained from hospital records.
Results: Maternal inflammatory response was seen in all 30 cases, with Stage 2 being the most frequent pattern (56.7%). Fetal inflammatory response was identified in 46.7% of cases. Funisitis was present in 30% of cases, including necrotizing funisitis in 6.7%. Cases showing isolated maternal inflammatory response were generally associated with better neonatal outcomes. In contrast, cases with fetal inflammatory response, particularly those with funisitis, showed increased neonatal morbidity including low Apgar scores, respiratory distress, early-onset sepsis, and prolonged NICU stay.
Conclusion: Fetal inflammatory response appears to have a stronger association with adverse neonatal outcomes when compared to isolated maternal inflammation. Routine placental examination in preterm deliveries may help in identifying clinically unsuspected chorioamnionitis and assist in neonatal risk assessment.

KEYWORDS: Preterm birth; Chorioamnionitis; Placenta; Maternal inflammatory response; Fetal inflammatory response; Funisitis

INTRODUCTION

Preterm birth, defined as delivery before 37 completed weeks of gestation, continues to be an important cause of neonatal morbidity and mortality worldwide. Nearly one million neonatal deaths are reported annually due to complications related to preterm birth. Intrauterine infection and inflammation are recognised contributors to spontaneous preterm labour, and chorioamnionitis is one of the commonly associated pathological conditions. Chorioamnionitis may be clinically silent in many patients and is often identified only after histopathological examination of the placenta. Histologically, inflammatory changes are classified into maternal inflammatory response (MIR) and fetal inflammatory response (FIR). The presence of FIR generally indicates progression of inflammation into the fetal compartment and has been associated with poorer neonatal outcome. Although many studies have evaluated placental inflammation in preterm births, detailed clinicopathological correlation at the individual case level is still limited. The present case series was undertaken to evaluate the histopathological spectrum of chorioamnionitis in 30 preterm placentas and to study the association between maternal and fetal inflammatory responses and neonatal outcome.

MATERIALS AND METHODS

This retrospective case series was conducted in the Department of Pathology at a tertiary care centre during the period from 2024 to 2025. A total of 30 placentas from preterm deliveries were included in the study. Cases with gestational age less than 37 weeks and histopathological evidence of chorioamnionitis were selected. Clinical details including maternal age, gravida status, history of premature rupture of membranes, mode of delivery, oligohydramnios, intrauterine fetal demise, and twin gestation were collected from hospital records. Placental specimens were fixed in 10% buffered formalin.

Representative sections were taken from the membranes, placental parenchyma, and umbilical cord. Routine processing and hematoxylin and eosin staining were performed. Histopathological evaluation focused on inflammatory changes involving the fetal membranes, placental tissue, and umbilical cord. Inflammatory changes were classified into maternal inflammatory response and fetal inflammatory response according to established Redline criteria. Maternal inflammatory response was staged from 0 to 3 and fetal inflammatory response from 1 to 3. Descriptive analysis was performed to assess the distribution of inflammatory stages and associated neonatal findings.

RESULTS

Thirty cases of histologically confirmed chorioamnionitis were analysed (Figure 1-5). Maternal age ranged from 21 to 35 years, with most patients belonging to the third decade of life.

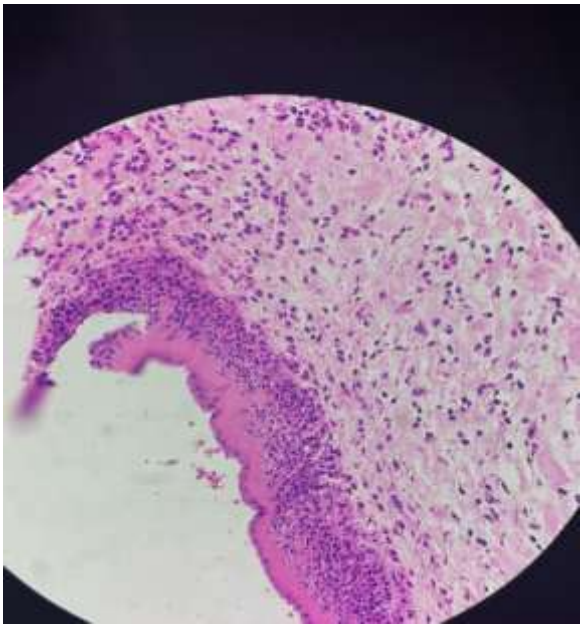

Figure 1: Advanced maternal inflammatory response (Stage 2) showing dense neutrophilic infiltration involving the amnion (H&E, ×200).

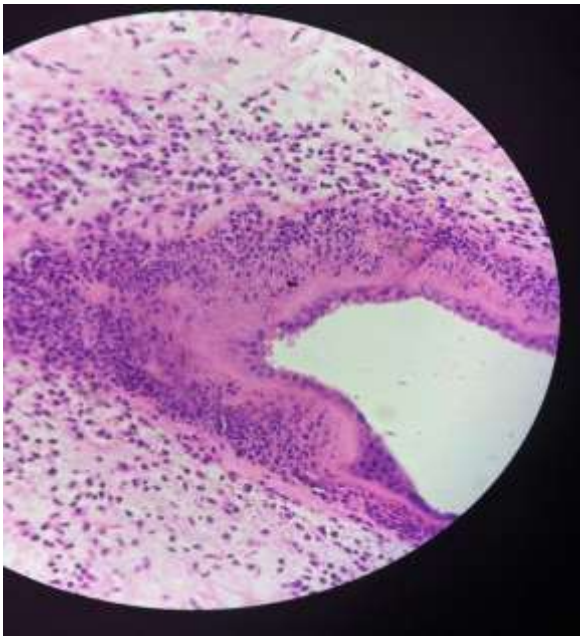

Figure 2: Progressive maternal inflammatory response with extension of neutrophils from chorion into amnion (H&E, ×200).

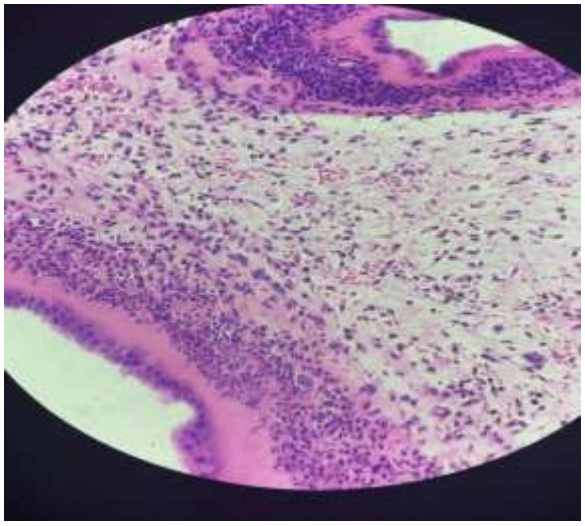

Figure 3: Diffuse neutrophilic infiltrate within placental stroma indicating active inflammation (H&E, ×200).

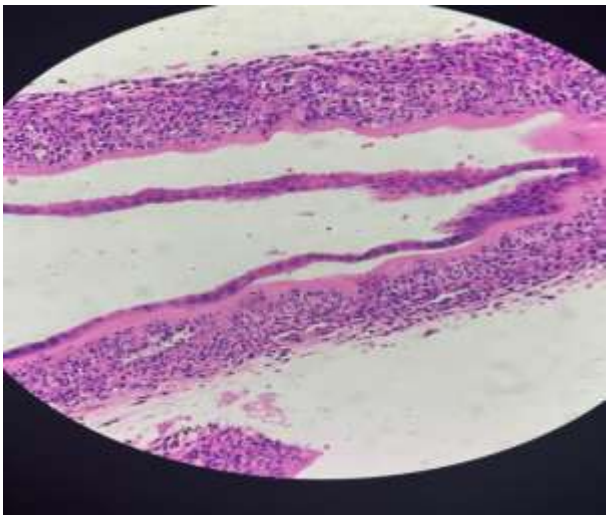

Figure 4: Early maternal inflammatory response with neutrophilic infiltration along fetal membranes (H&E, ×100).

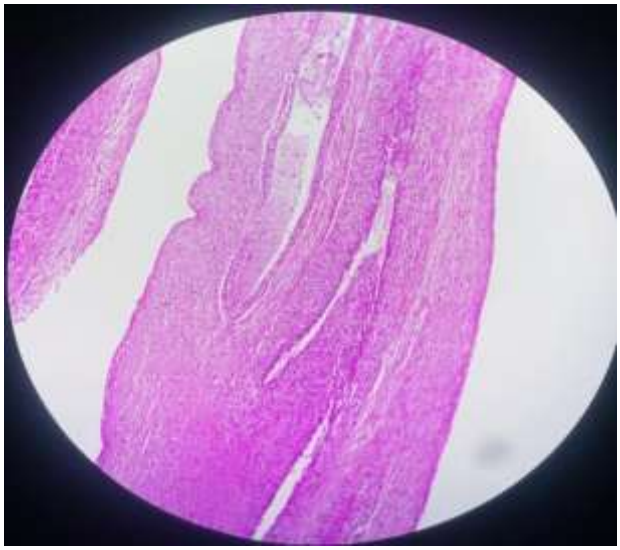

Figure 5: Funisitis showing neutrophilic infiltration of the umbilical cord (H&E, ×100).

Maternal inflammatory response was identified in all cases. Stage 2 MIR was the most common pattern and was seen in 56.7% of cases. Stage 1 was noted in 20% of cases, Stage 0–1 in 13.3%, and Stage 3 in 10% of cases. Fetal inflammatory response was present in 46.7% of cases. Among these, Stage 2 FIR was the most frequent pattern (23.3%), followed by Stage 1 (16.7%) and Stage 3 (6.7%). Umbilical cord involvement in the form of funisitis was observed in 30% of cases. Necrotizing funisitis was identified in 6.7% of cases and represented severe fetal inflammatory response (Figure 6). On clinicopathological correlation, cases with isolated maternal inflammatory response generally showed relatively favourable neonatal outcome. Cases showing fetal inflammatory response, especially those with funisitis, were more

commonly associated with neonatal complications such as low Apgar scores, respiratory distress, early-onset sepsis, and prolonged NICU admission.

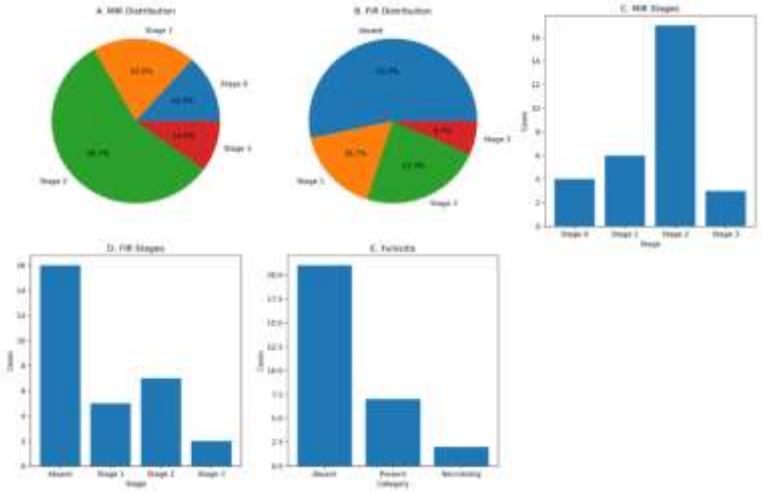

Figure 6. Histopathological spectrum of maternal and fetal inflammatory responses in chorioamnionitis (n = 30).

(A) Pie chart depicting the distribution of maternal inflammatory response (MIR) stages, showing Stage 2 as the predominant pattern (56.7%), followed by Stage 1 (20%), Stage 0 (13.3%), and Stage 3 (10%). (B) Pie chart illustrating the distribution of fetal inflammatory response (FIR), present in 46.7% of cases, with Stage 2 being most frequent (23.3%), followed by Stage 1 (16.7%) and Stage 3 (6.7%); FIR was absent in 53.3% of cases. (C) Bar graph representing the absolute number of cases across MIR stages. (D) Bar graph showing the distribution of FIR stages in terms of case numbers. (E) Bar graph depicting umbilical cord involvement (funisitis), observed in 30% of cases, including necrotizing funisitis in 6.7%, indicative of severe fetal inflammatory response.

DISCUSSION

The present study evaluated the histopathological spectrum of chorioamnionitis in preterm placentas and correlated the inflammatory response with neonatal outcome. Maternal inflammatory response was present in all cases, while fetal inflammatory response was identified in 46.7% of the study group. These findings further support the established role of placental inflammation in the pathogenesis of spontaneous preterm birth and adverse neonatal outcomes[1-6]. Stage 2 MIR (56.7%) was the commonest histological pattern in our series. Similar conclusions have been made in investigations assessing placental inflammation in premature births where acute maternal inflammatory alterations indicate the earliest host response to ascending intrauterine infection. MIR is a marker of maternal immune activation, although its presence alone has not been consistently related with significant newborn morbidity, particularly in the absence of fetal involvement [3,4,7]. Fetal inflammatory response (FIR) was seen in 46.7% of our cases showing that the inflammation went beyond the fetal membranes into the fetal tissues. FIR presence is suggestive of a more advanced stage of chorioamnionitis and suggests fetal innate immune system activation. Romero et al. have shown that fetal inflammatory response syndrome (FIRS) is characterized by increased fetal inflammatory cytokines and is related to increased neonatal complications such as respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, neonatal sepsis and long term neurodevelopmental impairment [6]. A similar study by Lee et al. showed a correlation between increased intensity of fetal inflammation and microbial invasion of the amniotic cavity and poor newborn outcomes [8]. Our findings are highly consistent with these observations; neonates with FIR experienced higher rates of respiratory distress, early-onset sepsis, poorer Apgar scores and longer NICU stay compared to neonates with isolated maternal inflammation. Funisitis was observed in 30% of our cases, including necrotizing funisitis in 6.7%, representing severe fetal inflammatory involvement. Redline described funisitis as the histological hallmark of fetal inflammatory response syndrome and an indicator of fetal immune activation.[7] Numerous studies have demonstrated that funisitis is associated with higher circulating fetal cytokine concentrations, increased risk of neonatal sepsis, cerebral injury and adverse neurological outcomes [6-8]. The association between funisitis and poorer neonatal outcome observed in the present study therefore supports its role as an important prognostic histopathological marker. Another noteworthy finding was the detection of histological chorioamnionitis in several clinically unsuspected cases. Clinical diagnosis of chorioamnionitis is known to have limited sensitivity because many patients remain asymptomatic or demonstrate only subtle clinical manifestations. Consequently, placental histopathological examination remains the gold standard for confirming intrauterine inflammation and identifying subclinical infection that may otherwise remain undiagnosed [3,4]. Recent work by Brink et al. demonstrated that placental inflammatory lesions differ between spontaneous and medically indicated preterm births and provide valuable insight into the underlying mechanisms of preterm delivery[5]. Similarly, Liu et al. showed that acute placental inflammatory lesions are associated with adverse neonatal outcomes and may serve as useful postnatal biomarkers for identifying preterm infants at increased risk of complications [9]. Routine pathological examination of placentas from preterm deliveries therefore provides valuable information for neonatal risk assessment and subsequent clinical management. The underlying pathophysiology involves ascending microbial invasion of the amniotic cavity, resulting in activation of maternal and fetal inflammatory pathways. Release of pro-inflammatory cytokines, chemokines, and prostaglandins stimulates uterine

contractility, cervical ripening, and membrane weakening, thereby contributing to spontaneous preterm labour. Continued progression of inflammation into the fetal compartment promotes systemic fetal inflammation, which is responsible for many of the adverse neonatal sequelae observed in affected infants[2,4,6].

This study adds to the clinicopathological data confirming the prognostic significance of differentiating maternal from fetal inflammatory responses on placental testing. The somewhat modest sample size nonetheless allowed meaningful correlation of comprehensive histological examination using recognized Redline criteria with newborn outcomes. But some limits should be noted. Our results may not be generalizable because of the retrospective methodology, small sample size, lack of microbiological culture and molecular investigations and lack of long-term neonatal follow-up. Future prospective studies with bigger patient cohorts and including microbiological, molecular and immunological markers are needed to better identify the prognostic importance of placental inflammatory lesions.

CONCLUSION

This case series highlights the usefulness of placental histopathology in identifying intrauterine inflammation in preterm deliveries. Maternal inflammatory response was observed in all cases, whereas fetal inflammatory response was present in nearly half of the cases and was commonly associated with neonatal morbidity.

The findings suggest that fetal inflammatory response, particularly funisitis, may have greater prognostic relevance than maternal inflammation alone. Routine placental examination in preterm deliveries can help in identifying clinically silent chorioamnionitis and may aid in neonatal risk stratification.

Further studies with larger sample size and long-term follow-up are required to better understand the prognostic significance of fetal inflammatory response.

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