# Placental inflammation in spontaneous preterm birth and neonatal outcomes

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## ABSTRACT

**Background:** Preterm birth (PTB) can be classified as spontaneous or indicated. The complications of PTB can affect all systems and result in chronic physical and mental disabilities. **Objective:** The objective of the study was to assess the incidence of placental inflammation in PTB with and without preterm premature rupture of membranes (pPROM) and its effects on various neonatal outcomes. **Materials and Methods:** This prospective observational study was conducted in a tertiary hospital where all preterm neonates born by spontaneous onset vaginal delivery and cesarean section were included in the study. Neonates born to mothers having significant uterine anomalies, multiple gestations, and those with any major congenital anomalies were excluded from the study. Placentas were assessed for evidence of inflammation on histopathological examination. Correlation of placental inflammation with neonatal morbidity and mortality was also assessed. **Results:** The incidence of placental inflammation in spontaneous onset preterm births (sPTB) was found to be 29%. Most placentas showed Stage 1 chorioamnionitis (47%). Three placentas had evidence of fetal inflammatory response, of which one had early funisitis (Stage 1) and two had intermediate funisitis (Stage 2). Of the nine neonates who had features of sepsis (definite or probable), 4 (44.4%) had evidence of placental inflammation. No significant association was found between placental inflammation and other secondary outcomes such as duration of neonatal intensive care unit stay, neonatal mortality, requirement of phototherapy, and need for continuous positive airway pressure support. **Conclusions:** Placental inflammation was seen in almost one-third of cases of sPTB, of which 78% were without pPROM. Hence, sPTB irrespective of pPROM should be considered as indirect marker of ongoing inflammation.

**Key words:** *Chorioamnionitis, Funisitis, Neonatal sepsis, Preterm premature rupture of membranes*

The incidence of preterm birth (PTB) has seen a steady increase worldwide over the past few decades and now ranges from 11 to 13% in most developed nations [1]. PTB can be classified as spontaneous or indicated. Spontaneous preterm birth (sPTB) includes (i) premature onset of labor which is defined as regular contractions with accompanying cervical changes but with intact membranes. (ii) Preterm premature rupture of membranes (pPROM) is defined as spontaneous rupture of membranes at <37 weeks of gestation and at least 1 h before the onset of contractions and is seen in 25–30% of PTB [1,2]. Indicated PTB is where labor is induced or delivery is by cesarean section performed for maternal or fetal indications [1-3]. The complications of PTB can affect all systems and result in chronic physical and mental disabilities [2]. The etiology of spontaneous preterm labor includes common causes such as multiple gestations, pPROM, hypertensive disorders of pregnancy (e.g., pre-eclampsia), antepartum hemorrhage (APH), cervical incompetence, and uterine malformations. The etiology of spontaneous onset preterm labor is still debated.

Microbiological studies indicate that intrauterine inflammation is associated with approximately 25–40% of all PTB [3]. Chorioamnionitis can present as a clinical condition defined by maternal fever, leukocytosis, and tachycardia, uterine tenderness, with or without pPROM. It can also be subclinical, which is considered as the most common manifestation and can be diagnosed histologically by inflammation of the chorion, amnion, and placenta. The inflammatory process is further classified into various stages and grades based on the severity.

The role of subclinical genital tract infection has long been implicated in the onset of spontaneous PTB. This infection leads to a cascade of inflammatory mediators which have been postulated to initiate the labor process [2-6]. The present study was done to assess the incidence of placental inflammation in PTB with and without pPROM and its effects on various neonatal outcomes.

## MATERIALS AND METHODS

This study was a prospective, observational study done in a tertiary hospital from November 2014 to July 2016. All preterm neonates born by spontaneous vaginal delivery and those born by cesarean section after spontaneous onset of labor were included in the study. Neonates born to mothers with uterine anomalies,

multiple gestations, and those having congenital anomalies were excluded from the study.

The incidence of placental inflammation in PTB from various studies has been found to be ranging from 37% to 48% [2-5]. To estimate the incidence of placental inflammation in spontaneous PTB with a 95% confidence interval and a relative precision of 25%, a sample size of 66 was required. A total of 66 neonates were enrolled in this study during the study period (Fig. 1).

The placentas of all neonates meeting the inclusion criteria were collected by a sterile technique and sent for examination to look for features of inflammation by a trained pathologist after initial processing and fixation. Features of placental inflammation were classified as maternal inflammatory response (MIR) or fetal inflammatory response (FIR). MIR consisted of subchorionitis and chorioamnionitis, whereas FIR included chorionic vasculitis, umbilical phlebitis or vasculitis, and necrotizing funisitis [4,5]. The term "stage" of inflammation refers to the progression of the inflammatory process based on the anatomical regions infiltrated by neutrophils and the term "grade" refers to the intensity of the acute inflammatory process at a particular site. The classification of inflammation used in the study was as per standard guidelines accepted worldwide by pathologists.

Ethical clearance was obtained from the Institutional Ethics Committee and an informed consent was taken from all mothers before enrolling them into the study. Neonates were followed after birth to assess various secondary outcomes, primarily evidence of sepsis, neonatal jaundice requiring phototherapy, incidence of respiratory distress syndrome (RDS), requirement of continuous positive airway pressure (CPAP), duration of hospital stay, and mortality. The comparison of various neonatal parameters with the presence of placental inflammation was done using Fisher's exact test and Chi-square test. SPSS 23 was used for statistical analysis. For all tests, $p<0.05$ was considered statistically significant.

## RESULTS

Demographic characteristics of the study population are depicted in Table 1. In our study group, the mean age of mothers was 26.3 years and the mean gestation period was 33.7 weeks. Among the study population, 86% of neonates were born by vaginal delivery and the rest were by cesarean section. pPROM was seen in 25.7% of mothers. The mean birth weight of neonates was 1.737 kg and mean gestational age was 33.3 weeks.

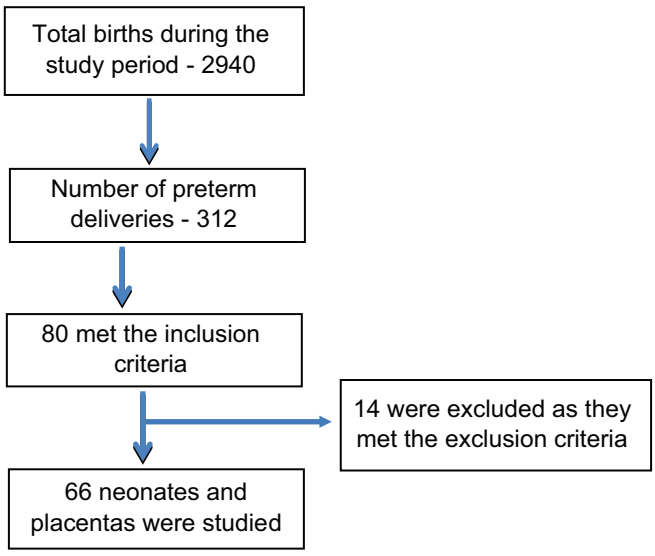


**Figure 1: Flowchart for inclusion of neonates into the study group**

Of the total 66 placentas sent for histopathological examination, 19 (29%) placenta showed evidence of inflammation. Of these, 15 mothers had preterm labor without rupture of membranes (Table 2). Most of the placentas showing placental inflammation had Stage 1 chorioamnionitis (47%) while Stage 2 and Stage 3 chorioamnionitis found in 15.6% and 21.1% cases, respectively. Placentas of three neonates showed evidence of FIR, of which one had Stage 1 (early funisitis) and the remaining two had Stage 2 (intermediate funisitis) FIR.

Of the nine neonates who had sepsis (definite or probable), 4 (44.4%) had evidence of placental inflammation on history and physical examination, which was not statistically significant (p=0.28). Of three neonates admitted to the neonatal intensive care unit (NICU) with definite sepsis, 2 (66.6%) had evidence of placental inflammation. Six neonates had probable sepsis, i.e., symptomatic neonates with sepsis screen positive and negative blood cultures; of which, 2 (33.3%) had evidence of placental inflammation. Of 66 neonates, 2 neonates died, and of them, 1 had evidence of placental inflammation. The cause of death in the other neonate was RDS and intraventricular hemorrhage (IVH).

The mean duration of NICU stay, of neonates having placental inflammation, was 22 days as compared to 16.4 days in those without it, which was not statistically significant. There was no significant association of placental inflammation with neonatal jaundice requiring phototherapy (p=0.78) and requirement of CPAP (p=0.40) (Table 3).

**Table 1: Antenatal characteristics of mothers**

| Characteristics | Subdivision | Number/ range | Mean±SD |
|---|---|---|---|
| Type of delivery | Vaginal delivery | 57 | |
| | LSCS | 09 | |
| Presence of pPROM | | 17 | |
| Duration of pPROM | <12 h | 10 | |
| | >12 h | 07 | |
| Antenatal use of antibiotics | | 19 | |
| Antenatal steroids | | 10 | |
| Gender | Male | 27 | |
| | Female | 39 | |
| Birth weight (kg) | | 0.60–2.78 | 1.74±0.432 |
| Gestational age (weeks) | | 24–36 | 33.30±2.266 |

**pPROM: Preterm premature rupture of membranes**

**Table 2: Placental inflammation and pPROM**

| Placental inflammation | pPROM absent | pPROM present | Total | p-value |
|---|---|---|---|---|
| Absent | 34 | 13 | 47 | 0.58 |
| Present | 15 | 04 | 19 | |
| Total | 49 | 17 | 66 | |

**pPROM: Preterm premature rupture of membranes**

**Table 3: Association of various neonatal outcomes with placental inflammation**

| Neonatal variable | Placental inflammation | | Total (n=66) | p-value |
|---|---|---|---|---|
| | Present | Absent | | |
| Sepsis | | | | 0.26 |
| Yes | 4 | 5 | 9 | |
| No | 15 | 42 | 57 | |
| Continuous positive airway pressure required | | | | 0.40 |
| Yes | 16 | 43 | 59 | |
| No | 3 | 04 | 7 | |
| Neonatal jaundice requiring phototherapy | | | | 0.76 |
| Yes | 3 | 6 | 9 | |
| No | 16 | 41 | 57 | |
| Neonatal mortality | | | | 0.50 |
| Yes | 1 | 1 | 2 | |
| No | 46 | 18 | 64 | |

## DISCUSSION

The incidence of PTB in our hospital was 10.2%, of which 2.7% deliveries were spontaneous onset preterm deliveries (sPTB) without any secondary causes such as multiple gestation, cervical incompetence, and APH. The incidence of placental inflammation in sPTB in our study was 29% as compared to a higher incidence ranging from 35% to 50% from other studies. The role of placental inflammation on neonatal morbidity and mortality has been proved beyond doubt based on scientific evidence [7-10]. The inflammatory process that leads to release of various inflammatory mediators, especially in FIR syndrome (FIRS), results in multiple organ involvement [3].

Watterberg *et al.* demonstrated that infants exposed to chorioamnionitis had a lower risk of developing RDS and an increased risk of bronchopulmonary dysplasia [10]. A study by Lahra *et al*. involving 724 preterm infants of <30 weeks' gestational age showed that the presence of chorioamnionitis with umbilical vasculitis was associated with a marked greater reduction of RDS when compared to chorioamnionitis alone [11]. A large number of studies have identified potential mechanisms for associations between chorioamnionitis and adverse neurological outcomes such as perinatal brain injury, cerebral palsy (CP), periventricular leukomalacia, and IVH. Chorioamnionitis has also been linked to higher incidence of speech delay, hearing loss, autism spectrum disorders, and schizophrenia [12-15].

Higher rates of retinopathy of prematurity have been demonstrated in infants born to mothers with histological and clinical chorioamnionitis relative to mothers without chorioamnionitis. [14]. Clinical data demonstrating an effect of chorioamnionitis on the developing kidney are limited. In a study of women with pPROM, FIRS was found to be associated with oligohydramnios [8].

Although there is enough evidence as stated above regarding the detrimental effects of placental inflammation on neonatal outcomes, our study could not establish a significant association between the two. A possible explanation for such findings could be a smaller sample size of our study as compared to other studies on this topic.

There have been laid down guidelines on the use of prophylactic antibiotics in pPROM, but their role in sPTB without rupture of membranes is still unclear [16,17]. In the Oracle II study, 6295 women with spontaneous preterm labor with intact membranes without evidence of clinical infection were randomly given antibiotics (erythromycin and co-amoxiclav) or placebo and neonates were assessed for outcomes and it was found that a marginally non-statistically significant increase was seen in functional impairment and CP in children whose mothers were given antibiotics in the antenatal period [18]. In the subgroup analysis, CP was statistically significantly increased for infants of women allocated to macrolide and beta-lactam antibiotics combined compared with placebo. In the Cochrane systematic review of antibiotics used to inhibit spontaneous preterm labor and PTB in women with intact membranes, no statistically significant benefit from antibiotic administration was demonstrated in any of the pre-specified neonatal outcomes including perinatal mortality.

In a developing country like ours, the mild subclinical vaginal leaks during pregnancy often go unattended due to ignorance and poor health facilities. These leaks can be a major contributor to the onset of sPTB resulting in greater neonatal morbidity and mortality.

The strengths of our study are that it is one of the very few Indian studies done to assess placental inflammation in sPTB and its association with neonatal outcomes. Furthermore, histopathological examination of placenta was done to define placental inflammation which is among the most objective ways of defining inflammation. The limitations of our study were its small sample size and the absence of a control group. Furthermore, placental and amniotic fluid cultures were not done in our study. These cultures would have further increased the rate of detection of placental inflammation.

## CONCLUSIONS

This study reveals that placental inflammation is commonly seen in spontaneous onset PTB. This was seen in almost one-third of cases

of spontaneous onset PTB, of which 78% did not have pPROM. Considering the implications of PTB in neonatal mortality and morbidity, prophylactic antibiotics could well be the answer in future though, evidence may not be in their favour at present.

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