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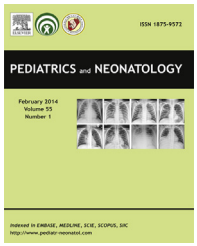

ORIGINAL ARTICLE

Effects of Placental Inflammation on Neonatal Outcome in Preterm Infants

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Background: Intrauterine infection is the most commonly identified cause of preterm birth. In this study, our aim was to determine the association between placental inflammation and neonatal outcome in a prospective observational cohort of preterm infants of less than 34 weeks gestational age. We especially focused on the distinct effects of maternal inflammatory response (MIR) with and without fetal inflammatory response (FIR).
Methods: Clinical characteristics and placental histological results were prospectively collected from 216 singleton infants born at a gestational age of less than 34 weeks.
Results: Of the 216 newborns, 104 (48.1%) infants had histological placental inflammation. Based on their pathological findings, the premature infants were divided into three groups: (1) the MIR negative–FIR negative (MIR−FIR−) group; (2) the MIR positive–FIR positive (MIR+FIR+) group; and (3) the MIR positive–FIR negative (MIR+FIR−) group. The incidence of neonatal respiratory distress syndrome (RDS) in the MIR+FIR− group (5.7%) and in the MIR+FIR+ group (2.0%) was significantly lower than in the MIR−FIR− group (19.6%) ($p < 0.05$). Logistic regression analysis showed that MIR+FIR+ group had a decreased incidence of neonatal RDS (OR = 0.076; 95% CI 0.009–0.624; $p = 0.016$). The incidence of intraventricular hemorrhage (IVH) Grade 2 or greater was significantly higher in the MIR+FIR+ group (42.3%) than in the MIR+FIR− group (13.0%) ($p < 0.05$) or in the MIR−FIR− group (15.2%) ($p < 0.05$). Logistic regression analysis also showed that MIR+FIR+ was associated with an increased incidence of IVH Grade 2 or greater (OR = 4.08; 95% CI 1.259–13.24; $p = 0.019$).

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Conclusion: A positive MIR in association with a positive FIR decreases the risk of RDS, but increases the risk of IVH Grade 2 or greater in preterm infants with a gestational age of less than 34 weeks. However, a positive MIR alone has little effect on neonatal outcome.

1. Introduction

Preterm birth remains an important cause of neonatal mortality and longterm morbidity, despite enormous advances in neonatal intensive care.[1] Intrauterine infection is the most common identified cause of preterm birth; chorioamnionitis is present in approximately 40—70% of women who deliver prematurely.[2] Chorioamnionitis is primarily the result of ascending bacteria from the vagina and cervix. Most identified pathogens in the uterus that are associated with preterm labor are of vaginal origin. Examples of such pathogens are *Ureaplasma urealyticum, Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma hominis*, Group B *Streptococcus*, and *Trichomonas vaginalis*.[3] An uncommon pathway of intrauterine infection is by bloodborne spread. Pathogenic colonization of the intrauterine space leads to placental inflammatory response, which is associated with preterm labor.

Two well-characterized types of placental inflammation are: (1) the maternal inflammatory response (MIR), which includes subchorionitis, chorionitis or chorioamnionitis; and (2) the fetal inflammatory response (FIR), which includes chorionic vasculitis, umbilical phlebitis or vasculitis, (subacute) necrotizing funisitis, or concentric umbilical perivasculitis.[4,5] Some studies indicate that MIR and/or FIR are associated with preterm birth and neonatal prematurity complications such as respiratory distress syndrome (RDS), chronic lung disease, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH).[6,7] However, there are few reports in China on the effects of placental inflammation (identified by histopathological examination) on neonatal outcome.

In this study, our aim was to determine the association between placental inflammation and neonatal outcome in a prospective observational cohort of preterm infants with a gestational age of less than 34 weeks. We especially focused on the distinct effects of MIR with and without FIR.

2. Methods

The effects of placental inflammation on neonatal outcome in preterm infants were explored in pregnant women who delivered preterm infants between January 2008 and October 2010 at the International Peace Maternity and Child Health Hospital of China Welfare Institution (Shanghai, China). Eligibility requirements were that an infant had to be a singleton, alive, and born before 34 weeks of gestation. Women with multiple-gestation pregnancies and newborns with major birth defects were excluded. The medical ethics committee of the hospital approved the study and all patients provided written consent.

2.1. Clinical characteristics of the study population

The prenatal, perinatal, and neonatal data were collected and stored in a database. Neonates who were transferred to another hospital were followed to complete the data record. The demographic and clinical variables examined included gestational age, birth weight, intrapartum management, and pregnancy complications.

We used the following clinical definitions in this study:

1. Gestational age at delivery was determined on the basis of the last menstrual period and early ultrasound findings (i.e., before 20 weeks of gestation).
2. Gestational hypertension was defined as new onset hypertension (i.e., blood pressure greater than 140/90 mmHg).
3. Fetal distress was diagnosed by the obstetrician and was based on cardiotocographic criteria.
4. A full course of prenatal steroid treatment was defined as 6 mg of dexamethasone delivered intramuscularly every 12 hours for a total of four times.
5. Respiratory distress syndrome (RDS) was defined as the presence of respiratory symptoms such as grunting and chest retraction, typical chest radiograph findings, and/or treatment with surfactant and the need for assisted ventilation (including nasal continuous positive airway pressure and mechanical ventilation).
6. Bronchopulmonary dysplasia (BPD) was defined as supplemental oxygen dependency at 36 weeks of corrected gestational age.
7. Patent ductus arteriosus (PDA) was suspected on the basis of clinical symptoms (e.g., systolic murmur, widened pulse pressure, hyperdynamic precordium) and confirmed by echocardiogram.
8. Necrotizing enterocolitis (NEC) was defined as stage II or above (using Bell's classification).
9. Retinopathy of prematurity (ROP) was defined according to the International Classification for Retinopathy of Prematurity.
10. A diagnosis of sepsis was based on the 2003 Kunming Neonatal Sepsis Definitions Conference criteria.[8] According to this conference, the diagnostic criteria for confirmed sepsis are a positive clinical/laboratory screen and a positive culture. Clinical sepsis was defined as a positive clinical/laboratory screen and negative cultures. Early-onset neonatal sepsis was recorded if it occurred during the first 72 hours after birth.
11. Intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) were defined by serial head ultrasound, performed according to the description by Volpe.[9] The first head ultrasound was performed within 3 days after birth and follow-up head ultrasound examinations were performed every week until the day of discharge.

2.2. Placental histopathological examination

Placentae and membranes were fixed in formalin immediately after delivery. Sampling included two membrane rolls, two cross-sections of the cord, and three blocks of the placental disk. The tissues were embedded in paraffin until histopathological examination. All placentae were examined for histologic evidence of inflammation by an experienced pathologist who was blinded to the clinical information. The placental inflammation was classified as maternal inflammatory response (MIR) and fetal inflammatory response (FIR) in accordance with the definition by the Amniotic Fluid Infection Nosology Committee.[5] The MIR includes subchorionitis, chorionitis, or chorioamnionitis. The FIR includes chorionic vasculitis, umbilical phlebitis or vasculitis, (subacute) necrotizing funisitis, or concentric umbilical perivasculitis.

2.3. Statistical analysis

Continuous data are presented as the mean ± standard deviation (SD). Dichotomous data are expressed by the frequency and associated percentage. Differences between groups were tested by analysis of variance (ANOVA) for continuous data or by the χ^2 test for dichotomous data. Logistic regression analysis was performed to identify risk factors for RDS and for IVH Grade 2 or greater. Significance was accepted at $p < 0.05$ (two-sided). All analyses were performed by using SPSS version 11.5 software (SPSS Inc, Chicago, IL).

3. Results

3.1. Placental pathology and perinatal characteristics

During the study period, 216 preterm (i.e., before 34 weeks of gestation), singleton live-born neonates were enrolled. Placental pathology showed that MIR was present in 104 (48.1%) mothers and that 51 (49.0%) infants of these mothers had signs of FIR. There were no cases of FIR without MIR. Based on the placental pathology, the study population was divided into 3 groups: (1) the MIR negative−FIR negative (MIR−FIR−) group; (2) the MIR positive−FIR positive (MIR+FIR+) group; and (3) the MIR positive−FIR negative (MIR+FIR−) group. Table 1 shows the perinatal clinical characteristics of the three groups. Between the three groups, there were no significant differences in gestational age; birth weight; sex; intrauterine distress; Apgar score at 1 minute of 7 or less; Apgar score at 5 minutes of 7 or less; or prenatal steroids use. The MIR+FIR− and MIR+FIR+ groups had significantly higher rates of preterm premature rupture of membranes, labor, and prenatal antibacterial therapy, compared to the MIR−FIR− group. Mothers in the MIR−FIR− group were conversely more likely to have gestational hypertension and deliver by cesarean section.

3.2. Placental inflammation and neonatal outcome

Table 2 shows the neonatal outcome parameters of the three groups. The incidence of transient tachypnea in the groups was not significantly different. However, the incidence of RDS, the use of nasal continuous positive airway pressure, and the use of mechanical ventilation was significantly lower in infants in the MIR+FIR− group or MIR+FIR+ group than in infants in the MIR−FIR− group. Placental inflammation (MIR or FIR) seemed to increase the risk of early-onset sepsis, but the change was not statistically significant.

Ninety-five infants completed serial head ultrasound examination, and 41 of the infants had brain injuries. Intraventricular hemorrhage occurred more often in the MIR+FIR+ group (57.7%) than in the MIR+FIR− group (34.8%) or the MIR−FIR− group (39.1%), but this difference was not statistically significant. Intraventricular hemorrhage Grade

Table 1 Perinatal clinical characteristics of the three groups.

Characteristics	MIR−FIR− (n = 112)	MIR+FIR− (n = 53)	MIR+FIR+ (n = 51)
Maternal age (y)	29.96 ± 4.54	29.91 ± 4.10	29.18 ± 5.05
Gestational age (d)	223.33 ± 11.60	220.83 ± 11.97	219.57 ± 10.97
Cesarean section	82 (73.2)	15 (28.3)*	18 (35.3)*
Labor	35 (31.3)	44 (83.0)*	36 (70.6)*
Male	65 (58.0)	35 (66.0)	25 (49.0)
Placental weight (g)	367.79 ± 90.01	401.44 ± 81.43*	400.04 ± 83.98
Birth weight (g)	1692.12 ± 443.37	1747.11 ± 371.52	1688.90 ± 392.00
Fetal distress	34 (30.4)	5 (9.4)	12 (23.5)
PPROM	30 (26.8)	31 (58.5)*	44 (86.3)*
Gestational hypertension	50 (44.6)	0 (0)*	2 (3.9)*
Prenatal antibacterial	43 (38.4)	39 (73.6)*	45 (88.2)*
Prenatal steroids			
None	11 (9.8)	7 (13.2)	5 (9.8)
Non-full course	59 (52.7)	19 (35.8)	27 (52.9)
Full course	42 (37.5)	27 (50.9)	19 (37.3)

FIR = fetal inflammatory response; MIR = maternal inflammatory response; PPROM = preterm premature rupture of membranes.
Data are expressed as n (%) or mean ± standard deviation.
* Compared to the MIR−FIR− group, $p < 0.05$.

Table 2 Neonatal outcome.

Outcome parameter *N* (%)	MIR−FIR− (*n* = 112)	MIR+FIR− (*n* = 53)	MIR+FIR+ (*n* = 51)
RDS	22 (19.6)	3 (5.7)*	1 (2.0)*
Transient tachypnea	16 (14.3)	5 (9.4)	11 (21.6)
Surfactant administered	66 (58.9)	23 (43.4)	23 (45.1)
Mechanical ventilation	45 (40.2)	11 (20.8)*	10 (19.6)*
BPD	7 (6.3)	7 (13.2)	3 (5.9)
Apgar score ≤7 at 1 min	28 (25.0)	7 (13.2)	8 (15.7)
Apgar score ≤7 at 5 min	8 (7.1)	2 (3.8)	3 (5.9)
PDA	8 (7.1)	3 (5.7)	3 (5.9)
NEC	4 (3.6)	1 (1.9)	2 (3.9)
ROP	0 (0)	0 (0)	0 (0)
Sepsis			
Early onset	8 (7.1)	6 (11.3)	8 (15.7)
Culture proven	0 (0)	2 (3.8)	2 (3.9)
Clinical sepsis	8 (7.1)	4 (7.5)	6 (11.8)
Late onset	26 (23.2)	12 (22.6)	18 (35.3)
Culture proven	12 (10.7)	4 (7.5)	9 (17.6)
Clinical sepsis	14 (12.5)	8 (15.1)	9 (17.6)
Death	6 (5.4)	3 (5.7)	1 (2.0)

BPD = bronchopulmonary dysplasia; FIR = fetal inflammatory response; MIR = maternal inflammatory response; NEC = necrotizing enterocolitis; PDA = patent ductus arteriosus; RDS = respiratory distress syndrome.
Data are expressed as *n* (%).
* Compared to the MIR−FIR− group, $p < 0.05$.

2 or greater occurred significantly more frequently in the MIR+FIR+ group than in the other two groups. The rate of cystic periventricular leukomalacia was not significantly different between the groups (Table 3).

In the multivariable model, the MIR+FIR+ group had a significantly reduced risk for RDS (odds ratio [OR] = 0.076; 95% CI 0.009−0.624; $p = 0.016$), when adjusted for gestational age, gestational hypertension, and labor. The MIR+FIR− group also seemed to have decreased odds for RDS, after controlling for potential confounders, but the difference was not statistically significant (OR = 0.279, 95% CI 0.069−1.125, $p = 0.073$). When adjusted for gestational age, birth weight and early onset sepsis, the MIR+FIR+ group had an increased risk of IVH Grade 2 or greater (OR = 4.08; 95% CI 1.259−13.24; $p = 0.019$). The MIR+FIR− group did not have an increased risk of IVH Grade 2 or greater (OR = 0.85; 95% CI 0.193−3.74; $p = 0.83$).

4. Discussion

4.1. Placental inflammation in preterm birth

This study showed that 48.1% of preterm infants were exposed to prenatal intrauterine inflammation, which is in line with the results of other reports.[10,11] There was interestingly no infant with only FIR in the study population, although FIR without MIR is believed to occur rarely and via the blood stream.[2] Intrauterine inflammation, which includes maternal and fetal responses to infection, is associated with preterm delivery.[12] Our findings of increased preterm premature rupture of membranes associated with maternal and fetal inflammation are in agreement with these previous reports.[11,13] Fetal inflammation in the placenta is regarded as the more serious type of intrauterine inflammation.

Table 3 Neonatal brain injury in three groups.

	MIR−FIR− (*n* = 46)	MIR+FIR− (*n* = 23)	MIR+FIR+ (*n* = 26)
IVH (all grades)	18 (39.1)	8 (34.8)	15 (57.7)
IVH (Grade II−IV)	7 (15.2)	3 (13.0)	11 (42.3)*
IVH (Grade III−IV)	3 (6.5)	1 (4.3)	4 (15.4)
Cystic PVL	2 (4.3)	0 (0)	0 (00)

FIR = fetal inflammatory response; IVH = Intraventricular hemorrhage; MIR = maternal inflammatory response; PVL = periventricular leukomalacia.
Data are expressed as *n* (%).
* Compared to the other two groups, $p < 0.05$.

4.2. Placental inflammation and respiratory distress syndrome

In this study, univariate analyses showed that placental inflammation was associated with a decreased incidence of RDS, whether MIR was associated with or without FIR. However, after multivariable adjustment, only MIR with FIR showed a reduced incidence of RDS.

Watterberg et al[14] reported that exposure to placental inflammation decreased the risk of RDS. Since their report, many researchers have explored the relationship between placental inflammation and RDS, but the results of these studies have been inconsistent.[15,16] Kaukola et al[17] demonstrated in a prospective cohort that histological chorioamnionitis was associated with a lower risk of RDS; however several studies have reported no relationship between placental inflammation and RDS.[8,19] Furthermore, these studies did not subdivide the study population according to the presence or absence of FIR.[17–19]

A large cohort study of 724 preterm infants of less than 30 weeks gestational age showed that the presence of chorioamnionitis with umbilical vasculitis was associated with a markedly greater reduction of RDS than was chorioamnionitis alone.[10] Our data suggest that the additional presence of FIR in the placenta can provide the protective effect against neonatal RDS in preterm infants that are less than 34 weeks gestational age, but MIR alone has little effect on RDS.

Animal experiments have demonstrated that prenatal inflammation exposure can induce maturation of fetal lungs.[20] For instance, intra-amniotic injection of endotoxin can produce intrauterine inflammation and elicit the production of surfactant proteins in the fetal lung.[21] Intra-amniotic interleukin-1 (IL-1)[22] and ureaplasma[23] also induce lung maturation in fetal sheep.

4.3. Placental inflammation and brain injury

Common neonatal brain injuries of preterm infants are IVH and white matter disease (WMD), which comprises cystic and noncystic periventricular leukomalacia (PVL). Magnetic resonance imaging recently indicates that noncystic PVL accounts for most cases of WMD.[24] The incidence of cystic PVL has progressively decreased. Several studies show that chorioamnionitis with or without fetal involvement was associated with neonatal brain injury, including WMD and IVH.[25,26] A meta-analysis of observational studies by Wu et al[27] also reports that clinical chorioamnionitis was associated with cystic PVL and cerebral palsy.

In the present study, univariate analyses showed MIR with FIR was associated with an increased incidence of IVH Grade 2 or greater. The effect furthermore remained after adjusting for gestational age, birth weight, and early onset sepsis. In this population of preterm infants, 1% (2/216) of the neonates experienced cystic PVL. We found no influence of placental inflammation on WMD, as other studies have reported. This inconsistency may be attributable to the lower sensitivity of cranial ultrasound in detecting noncystic PVL and the relatively older age of our study population.

Intrauterine inflammation can potentially lead to FIR and increase the local production of cytokines in the fetal brain, thereby damaging the blood–brain barrier.[28] An animal study showed that intrauterine Lipopolysaccharide induced the immune response in the placenta and in the fetal brain, which significantly decreased dendritic counts in cortical cultures.[29]

4.4. Placental inflammation and sepsis or other neonatal diseases

Sepsis greatly contributes to the mortality and morbidity of preterm infants. Early onset sepsis is typically associated with vertical transmission of infection from the mother to her infant and is often caused by organisms that colonize the maternal genitourinary tract. A cohort study of 3094 infants showed that clinical chorioamnionitis was associated with a 5.5-fold increase in the incidence of early onset sepsis.[30] Several studies also indicate that histologic chorioamnionitis seemed to increase the risk of early onset sepsis in preterm infants.[26,31,32] In the present study, the trend of increasing neonatal early onset sepsis was present in the intrauterine inflammation-exposed newborns, although the difference was not statistically significant.

Bronchopulmonary dysplasia (BPD) is one of the most frequent sequelae in very preterm infants. A systematic review and meta-analysis suggest that chorioamnionitis was significantly associated with BPD.[33] However, there was no association between placental inflammation and the incidence of BPD in the present cohort study. A possible explanation for the discrepancy is that the patient population of our study was relatively older.

5. Conclusion

A positive MIR with a positive FIR decreases the risk of RDS but increases the risk of IVH Grade 2 or greater in preterm infants with a gestational age of less than 34 weeks. However, a positive MIR alone has little effect on neonatal outcome.

Conflicts of Interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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