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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.