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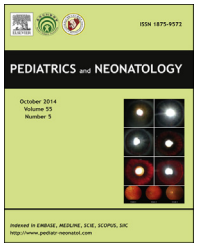

ORIGINAL ARTICLE

Morbidity and Mortality Among Very-low-birth-weight Infants Born to Mothers with Clinical Chorioamnionitis

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Key Words
clinical chorioamnionitis;
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newborn;
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periventricular leukomalacia

Background: Controversy exists about the relationship between maternal inflammation and the development of different morbidities and mortality in the newborn. We aimed to establish the incidence of clinical chorioamnionitis in our Neonatal Intensive Care Unit and its relation to morbidity and mortality among very-low-birth-weight infants.
Methods: This was an observational study of a cohort of very-low-birth-weight neonates admitted to our Neonatal Intensive Care Unit, between January 2008 and December 2012. Demographic characteristics and outcomes were analyzed and a comparison between exposed and non-exposed infants was carried out.
Results: During the study period, 451 very-low-birth-weight infants were admitted to our Neonatal Intensive Care Unit, and 31 (6.87%) were exposed to maternal clinical chorioamnionitis. The incidence was higher at lower gestational ages: 13.2% (23–26 weeks), 8.1% (27–30 weeks), and 2.6% (31–34 weeks) ($p = 0.022$). After correcting by gestational age and birth weight, early-onset neonatal sepsis (adjusted relative risk = 6.13; 95% confidence interval = 1.67–22.58; $p = 0.006$) and periventricular leukomalacia (adjusted relative risk = 24.62; 95% confidence interval = 1.87–324.28; $p = 0.015$) were significantly associated with maternal clinical chorioamnionitis. There were no differences in mortality or in survival without major morbidity.
Conclusion: Clinical chorioamnionitis confers an increased risk of early-onset neonatal sepsis and periventricular leukomalacia to exposed very-low-birth-weight infants.

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1. Introduction

Chorioamnionitis is an intrauterine inflammatory condition, mainly caused by bacterial invasion of the amniochorionic membranes. It can lead to a fetal inflammatory response that contributes to multi-organ injury, and it is frequently involved in the origin of the preterm premature rupture of membranes and spontaneous preterm birth, especially at the earliest gestational ages (GAs).[1,2]

Frequently the inflammation is subclinical, but histological, biochemical, or microbiological findings can be present. The clinical diagnosis is usually based on the presence of maternal fever, maternal or fetal tachycardia, uterine tenderness, foul smelling vaginal discharge, and maternal leucocytosis or elevated C-reactive protein, but the criteria vary among studies.

Chorioamnionitis has been considered a risk factor for neonatal sepsis, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, retinopathy of prematurity (ROP), and developmental delay.[3,4] However, it was reported some years ago that histological but not clinical chorioamnionitis decreases the incidence and severity of RDS, although it may increase the susceptibility to BPD.[5] Recent studies, however, seem to confirm the effect of chorioamnionitis on the incidence of RDS, but no effects on BPD are appreciated.[6] Furthermore, some studies could not demonstrate any association with these morbidities or with mortality, mainly after adjusting by GA.[4,7,8] Differences in definitions and inclusion criteria, together with changes in clinical practice, could be the reasons for such discrepancies, and controversy still persists. Other important methodological problems of previous studies were retrospective design, and the lack of power to detect confounder factors that could alter the relationship between clinical chorioamnionitis and neonatal outcomes.

Therefore, we conducted a prospective study with the objective to determine the incidence of clinical chorioamnionitis in our population, its association with GA at birth, and its effects on neonatal morbidity and mortality in a large cohort of very-low-birth-weight (VLBW) infants.

2. Methods

This was an observational, prospective study of a cohort of VLBW neonates who were born in our maternity and/or admitted to our Neonatal Intensive Care Unit in the first 28 days of life, between January 2008 and December 2012. We included all consecutive newborn infants with a birth weight $\leq$1500 g and/or $<$30 weeks of gestational age. Data were collected systematically according to a preestablished protocol until death or discharge from hospital. All records were supervised by one investigator (F.G.-M.R.). The study protocol was approved by the Institutional Review Board.

Clinical chorioamnionitis was defined according to adapted Gibbs criteria,[9] as maternal fever $\geq$38°C at least on two occasions separated by 1 hour, plus as least two of the following: uterine tenderness defined as pain referred by the mother on abdomen palpation in the absence of uterine contractions, leucocytosis ($>$15,000 cells/mm^3), maternal tachycardia ($>$100 bpm), fetal tachycardia ($>$160 bpm), or foul smelling vaginal discharge.

GA was established according to the best available obstetric estimation, taking into account the maternal last menstrual period, obstetrical parameters, and an early prenatal ultrasound. If necessary, GA was also assessed by the attending neonatologist on the basis of physical criteria and/or neurological examination (new Ballard score).[10] GA was recorded in completed weeks.

Maternal and neonatal demographic data were collected, including maternal age, parity, prenatal care and morbidities (diabetes, hypertension, etc.), multiple or single gestation, antenatal steroids and antibiotics administration, type of delivery and resuscitation, GA, birth weight, sex, Apgar score at 1 minute and 5 minutes, and admission temperature.

Neonatal morbidity was compared between exposed and non-exposed infants, including the following: RDS (defined by the presence of respiratory symptoms, the need of oxygen or invasive or non-invasive mechanical ventilation, and a compatible chest X-ray in the first 24 hours), patent ductus arteriosus (PDA) detected by ultrasonography, early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS; bacterial infection documented by a positive blood culture in the first 72 hours or after that, respectively), necrotizing enterocolitis (NEC) defined according to Bell's criteria (stage $\geq$2),[11] severe IVH (defined as Grades 3 and 4 by Papile et al[12]), PVL, BPD (dependency of oxygen supplementation at 36 weeks' postmenstrual age), and ROP ($>$2 stage). We also analyzed and compared total length of stay, survival, and survival without major morbidity (major morbidity includes any of the following: severe IVH, PVL, BPD, NEC, or ROP $>$2 stage).

2.1. Data analysis

Statistical analyses were performed with SPSS-19 software (SPSS Inc., Chicago, IL, USA). Normality of data was assessed with the Kolmogorov—Smirnov test. Centralization measures are expressed as mean and standard deviation (SD). Mean comparisons between groups were performed

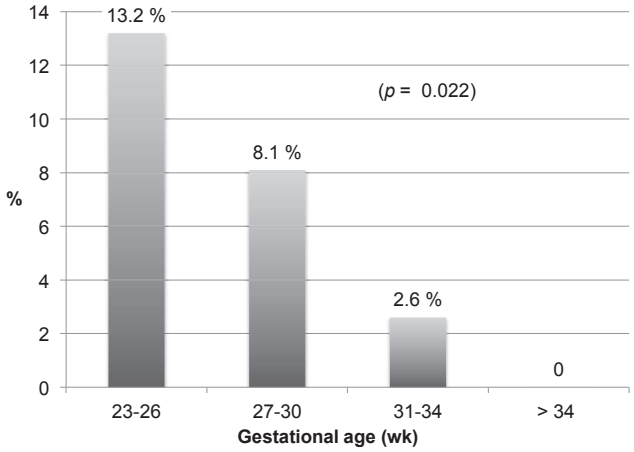

Figure 1 Incidence of clinical chorioamnionitis according to gestational age.