

Effect of maternal clinical chorioamnionitis on neonatal morbidity in very-low birthweight infants: a case-control study

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Abstract

Aims: To assess the relationship between maternal clinical chorioamnionitis and neonatal outcome in preterm very-low birthweight (VLBW) infants.

Methods: An observational case-control study was conducted in the Neonatology Services of 12 acute-care teaching hospitals in Spain. Between January 2004 and December 2006, all consecutive VLBW (≤ 1500 g) infants born to a mother with clinical chorioamnionitis were enrolled. Controls were infants without chorioamnionitis matched by gestational age who were born immediately after each index case.

Results: There were 165 cases and 163 controls. A significantly higher percentage of cases than controls required intubation (53% vs. 35.8%), had normal intrauterine growth (98.1% vs. 84.7%), were born in a tertiary center (inborn) (95.1% vs. 89.1%), from single gestations (76.4% vs. 65.6%) and vaginal delivery (47.3% vs. 33.3%), showed a lower

Apgar score at 5 min, and presented a higher rate of early-onset sepsis (10.4% vs. 1.2%). Older maternal age (32.5 vs. 30.8 years), premature labor (67.3% vs. 25.8%), premature rupture of membranes (61.3% vs. 25.8%), and antibiotic treatment (88.5% vs. 52.3%) were significantly more frequent among cases than controls.

Conclusions: After controlling by gestational age, maternal chorioamnionitis was associated with neonatal depression and early sepsis but not with other prematurity-related complications.

Keywords: Chorioamnionitis; fetal membranes; infant, premature; premature birth; premature rupture.

Introduction

Chorioamnionitis is considered to be one of the main causes of preterm delivery and has been associated with adverse perinatal outcomes in preterm infants. Preterm delivery remains a major obstetric problem, accounting for 70% of perinatal mortality and nearly 50% of long-term neurologic morbidity [5]. In recent years, a great deal of attention has turned to the impact of antenatal inflammation on both short-term outcome and long-term sequelae in preterm infants. In addition to severe acute morbidity, including early-onset sepsis, necrotizing enterocolitis and lung disease [2, 14], the preterm infant is at considerable increased risk of developing intraventricular hemorrhage and periventricular leukomalacia, which, in turn, is a strong predictor of mental retardation and cerebral palsy [8, 22, 23]. Histological chorioamnionitis is associated with a decreased incidence of respiratory distress syndrome, whereas the incidence of bronchopulmonary dysplasia is increased [1]. On the other hand, full-term babies exposed to intrauterine infection often present with depressed Apgar scores and neonatal encephalopathy, and are at marked increased risk of developing cerebral palsy.

On the basis of the close association between infection and very preterm birth, some authors have proposed that chorioamnionitis plays a causal role not only in the induction of delivery, but also in producing the fetal inflammatory response syndrome, which is also considered as the cause of acute morbidity as well as long-term sequelae in the infant [8, 18]. Different studies have examined the effects of clinical maternal chorioamnionitis and histological chorioamnionitis on neonatal and neurodevelopmental outcome in preterm babies [13, 19–21]. However, the interpretation of these studies is complicated by the fact that important confounders, such as gestational age have not been adjusted for

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in the analysis. Therefore, a case-control study in which cases and controls were matched by gestational age was designed to assess the relationship between maternal clinical chorioamnionitis and neonatal outcome in very-low birth-weight (VLBW) preterm infants.

Methods

Between January 2004 and December 2006, the Neonatology Services of 12 acute-care university-affiliated hospitals throughout Spain participated in an observational, prospective, case-control study. Cases were all consecutive preterm infants weighing ≤ 1500 g who were born to a mother with history of clinical chorioamnionitis. Controls were infants without such history matched by gestational age, who were born subsequently to each index case. The diagnosis of clinical chorioamnionitis in the pregnant woman who presented with premature labor or premature rupture of the membranes was made in the presence of uterine pain, fever ($\geq 38^\circ\text{C}$), leukocytosis ($> 12,000$ cells/mm³), and increased serum concentrations of C-reactive protein (> 30 mg/L). Common clinical manifestations, such as malodorous vaginal discharge and maternal or fetal tachycardia were not included as diagnostic criteria of clinical chorioamnionitis in the study protocol. Infants with chromosomal or congenital abnormalities were excluded from the study. The study was approved by the Institutional Review Board of each participating center, and written informed consent from the parents for data collection was obtained. The inclusion of cases and controls in the study did not involve any intervention. Infants received individualized standard care according to current clinical guidelines.

A study protocol was designed in which the following data were prospectively recorded: maternal age; premature labor (persistent uterine contraction, morphological changes in the cervix); premature rupture of membranes (clinical or biochemical evidence of amniorrhexis); intrapartum antibiotic treatment; antenatal steroid therapy (one or more course of betamethasone); cesarean delivery; multiple gestation; and whether the birth occurred in or outside the tertiary care center (inborn, outborn). Preterm labor was usually defined as regular contractions accompanied by cervical changes at < 37 weeks' gestation [4]. Morphological changes in the cervix included 2 cm dilatation or short cervical length (< 25 mm) [9]. Premature rupture of membranes was defined as spontaneous rupture of membranes at < 37 weeks' gestation at least 1 h before the onset of contractions. Diagnosis can be made clinically by evidence of amniotic fluid in the vagina (pH testing, fluorescein injection) or biochemically (fetal fibronectin testing) [3]. Newborn data included gestational age, sex, weight at birth, intrauterine growth restriction (IUGR) (below the 10th percentile using race- and sex-specific growth charts); need of resuscitation maneuvers in the delivery room using endotracheal intubation, and Apgar score at 5 min. Neonatal morbidity and mortality data included the presence of respiratory distress syndrome, patent ductus arteriosus (and surgical correction), necrotizing enterocolitis (and surgical treatment), seizures, early-onset sepsis, late-onset sepsis, fungal sepsis, intraventricular hemorrhage (and severe intraventricular hemorrhage grades III and IV), periventricular leukomalacia, bronchopulmonary dysplasia or oxygen requirement at 28 days, chronic lung disease or oxygen requirement at a corrected age of 36 weeks gestation, retinopathy of prematurity (grade ≥ 2) (and laser treatment), death, and survival without chronic lung disease. The length of hospital stay was also recorded.

The Kolmogorov-Smirnov test was used to evaluate the distribution of data. Normally distributed data are expressed as mean and standard deviation (SD) and otherwise as median and interquartile (25th–75th percentile) range. Categorical variables are expressed as absolute numbers and percentages. Differences between cases and controls were assessed with the Mann-Whitney *U*-test or one-way analysis of variance (ANOVA) for continuous variables, and the chi-square (χ^2) test for categorical variables. Odds ratio and 95% confidence intervals (CI) were calculated to assess the magnitude of the differences. The SPSS statistical package was used (version 12.0, SPSS Inc., Chicago, IL). *P*-value of < 0.05 was considered statistically significant.

Results

A total of 328 preterm babies weighing ≤ 1500 g were recruited during the study period, and grouped into 165 cases and 163 controls. Perinatal characteristics are shown in Table 1. Cases and controls were similar regarding weight at birth, gestational age, and sex. IUGR occurred less frequently in the group of infants with maternal chorioamnionitis than in controls. In this group there were also more inborns, singletons, and vaginal deliveries. Moreover, resuscitation with endotracheal intubation was needed more frequently and had a lower 5-min Apgar score. Premature labor, premature rupture of membranes, and antimicrobial therapy were also more frequent among cases than controls.

As shown in Table 2, morbidity and mortality was similar in both study groups. The only variable with significant differences was early-onset sepsis, which occurred in 10.4% of infants with maternal chorioamnionitis and in 1.2% in controls ($P=0.001$) (odds ratio 9.3, 95% CI 2.11–9.31). The mortality rate was 23% in cases and 17.2% in controls. The median length of hospital stay was 56 days in both cases and controls.

Discussion

In the present prospective case-control study of VLWB preterm infants, those born from mothers with clinical chorioamnionitis were more depressed at birth, required more often neonatal resuscitation and endotracheal intubation, and suffered from early-onset sepsis more frequently than controls. These findings are consistent with a previous case-control study carried out by our group on 135 newborns weighing < 1500 g at birth and born between 1988 and 1998 [7]. In this study, the cases comprised of 45 newborns exposed to clinical or subclinical levels of maternal chorioamnionitis. Each newborn in the case group was matched with two controls, both weighing < 1500 g, one of them born immediately before and the other immediately after. Perinatal records, neonatal morbidity and mortality were analyzed. Forty percent of the cases presented sepsis in the first 72 h of life compared with 10% of the controls ($P<0.0001$). In addition, resuscitation (77.8% vs. 45.6%, $P=0.001$) and mechanical ventilation (73% vs. 50%, $P=0.016$) were required by more cases than controls. The presence of cho-

Table 1 Perinatal characteristics of the study population.

Variables	Cases n = 165	Controls n = 163	P-value	Odds ratio (95% CI)
Maternal and labor data				
Maternal age, years, mean (SD)	32.5 (5.3)	30.8 (5.5)	0.006	
Premature labor	111 (67.3)	92 (56.4)	0.043	1.59 (1.01–2.48)
Premature rupture of membranes	98 (59.4)	41 (25.1)	<0.001	4.55 (2.82–7.33)
Antibiotic treatment	112 (67.9)	46 (28.2)	<0.001	20.45 (7.61–54.9)
Antenatal steroids	146 (88.5)	130 (79.7)	0.433	
Cesarean delivery	87 (52.7)	108 (66.2)	0.010	0.56 (0.36–0.88)
Multiple gestation	39 (23.6)	56 (34.4)	0.032	0.59 (0.36–0.96)
Inborn	156 (94.5)	145 (88.9)	0.039	2.42 (1.02–5.75)
Newborn data				
Males	86 (52.1)	91 (55.8)	0.501	
Gestational age, weeks, median (IQR)	28.0 (26.4–29.7)	28.7 (27–29.8)	0.107	
Birthweight, g, mean (SD)	1073 (246)	1040 (229)	0.216	
IUGR	13 (7.9)	25 (15.3)	0.035	0.47 (0.23–0.96)
Apgar score at 5 min, median (IQR)	8 (7–9)	9 (8–9)	<0.001	
Endotracheal intubation	87 (52.7)	58 (35.6)	0.002	2.03 (1.30–3.16)

Data as number and percentages unless otherwise stated.

CI = confidence interval, SD = standard deviation, IUGR = intrauterine growth restriction, IQR = interquartile range (25th–75th percentile).

riooamnionitis was associated with a higher risk of early onset infection and the need for neonatal resuscitation and mechanical ventilation.

Chorioamnionitis has been also associated with premature rupture of membranes. In a review of 430 singleton pregnancies with confirmed premature preterm rupture of membranes at 24 weeks or beyond that resulted in delivery at <37 weeks, composite neonatal major and minor morbidity rates were compared between pregnancies complicated by chorioamnionitis and those that were not [16]. Thirteen per-

cent of women with premature preterm rupture of membranes developed chorioamnionitis. The composite neonatal major morbidity rate was significantly higher in neonates whose mothers developed chorioamnionitis (55%) vs. those who did not (18%, $P < 0.0001$), and the incidence of chorioamnionitis increased significantly with decreasing gestational age. For this reason, in our study, cases and controls were matched by gestational age.

In a retrospective study on 452 preterm newborns <34 weeks at birth (mean birthweight 1440 g) that evaluated

Table 2 Morbidity and mortality during the neonatal period.

Variables	Cases n = 165	Controls n = 163	P-value
Respiratory distress syndrome	101 (61.2)	109 (66.9)	0.391
Patent ductus arteriosus	52 (31.5)	60 (36.8)	0.370
Surgical correction	13/52 (25)	8/60 (13.3)	0.114
Necrotizing enterocolitis	15 (9.1)	14 (8.6)	0.888
Surgical treatment	8/15 (53.3)	9/14 (64.3)	0.549
Seizures	7 (4.2)	5 (3.1)	0.554
Early-onset sepsis	17 (10.3)	2 (1.2)	0.001
Late-onset sepsis	59 (35.7)	52 (31.9)	0.458
Fungal sepsis	17 (10.3)	8 (4.9)	0.066
Intraventricular hemorrhage	44 (26.7)	45 (27.6)	0.928
IVH grade III–IV	17 (10.3)	21 (12.9)	0.502
Periventricular leukomalacia	26 (15.7)	21 (12.9)	0.373
Bronchopulmonary dysplasia	49 (29.7)	49 (30.1)	0.716
Chronic lung disease	18 (10.9)	27 (16.6)	0.232
Retinopathy of prematurity (grade ≥ 2)	18 (10.9)	14 (8.6)	0.311
Laser treatment	6/18 (33.3)	6/14 (42.8)	0.082
Death	38 (23.0)	28 (17.2)	0.186
Length of hospital stay, days, median (IQR)	56 (28–76)	56 (39.5–73)	0.538
Alive without chronic lung disease	106 (64.2)	106 (65.0)	0.874

Data as number and percentages unless otherwise stated.

IQR = interquartile range (25th–75th percentile).

the role of histological chorioamnionitis on the overall morbidity of preterm newborns, an association only between histological chorioamnionitis and cystic periventricular leukomalacia was observed [17]. In our study, examination of the placenta to confirm histological chorioamnionitis was not performed. However, the strength of association between histologic chorioamnionitis and preterm delivery has been inconsistent [10]. In another retrospective study of 100 women with singleton pregnancies between 22 and 28 weeks of gestation and with chorioamnionitis diagnosed on admission by amniotic fluid neutrophil elastase level, higher levels of this biochemical marker were associated with a shorter interval from admission to delivery [12]. In a retrospective comparison of adverse neonatal outcome of singleton pregnancies with documented premature rupture of membranes and chorioamnionitis (cases) with those who did not (controls), poor neonatal outcome was significantly associated with chorioamnionitis (34% vs. 13%, $P=0.008$), confirming that chorioamnionitis complicating premature rupture of membranes worsens neonatal outcome [15].

In contrast with studies with a retrospective cohort design, the present prospective case-control study suggests that after controlling for gestational age, complications, especially related to prematurity rather than to chorioamnionitis, did not appear to be significant. An increase in the occurrence of intraventricular hemorrhage, severe intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and chronic lung disease in the chorioamnionitis group was not observed. According to our findings, maternal chorioamnionitis was a risk factor for neonatal depression and early-onset sepsis.

Inflammation has been implicated in the mechanisms responsible for preterm and term parturition, as well as fetal injury. Most cases of histopathological inflammation and histological chorioamnionitis, both in preterm and term labors, are subclinical in nature, and the isolation of bacteria in the amniotic fluid is a pathological finding, the frequency of which is dependent upon the clinical presentation and gestational age [18]. The natural history of inflammation after premature rupture of membranes can be modified by antibiotic administration, although antibiotic administration rarely eradicates intra-amniotic infection in patients with preterm premature rupture of membranes; moreover, some patients with documented inflammation of the amniotic cavity show a decrease in the intensity of the inflammatory process after antibiotic administration [6]. Antenatal inflammation is very commonly associated with preterm deliveries, but there is generally minimal information about the duration, intensity, or organisms associated with chorioamnionitis. In preterm animal models, chorioamnionitis causes a lung injury similar to bronchopulmonary dysplasia and also causes clinical lung maturation. Continuous exposure of the developing lung before and after delivery to inflammation may be central to the development of bronchopulmonary dysplasia [11]. It might be plausible that antimicrobials and antenatal steroids in pregnant women with chorioamnionitis may decrease the inflammatory response. In the present series, 88.5% of women received antenatal steroids, which may account for the

favorable outcome of neonates in the chorioamnionitis group. However, the infectious/inflammatory mechanisms involved in acute neonatal morbidity and mortality in preterm infants exposed to chorioamnionitis are incompletely understood.

Although in this prospective clinical study the diagnosis of histological chorioamnionitis was not made, we conclude that after controlling by gestational age, maternal clinical chorioamnionitis was associated with neonatal depression and early-onset sepsis but not with other prematurity-related complications.

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