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Outcomes of Very-Low-Birth-Weight Infants Exposed to Maternal Clinical Chorioamnionitis: A Multicentre Study

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Key Words
Respiratory distress syndrome · Patent ductus arteriosus · Early-onset neonatal sepsis · Late-onset neonatal sepsis · Necrotizing enterocolitis · Mortality

Abstract
Background: Chorioamnionitis is a recognized risk factor of preterm delivery; however, controversy still persists concerning the relationship between maternal inflammation and neonatal morbidity and mortality. ***Objective:*** To determine the incidence of clinical chorioamnionitis and its relationship to morbidity and mortality among very-low-birth-weight (VLBW) infants. ***Methods:*** This was a retrospective analysis of prospectively collected data of VLBW neonates ≤32 weeks' gestational age (GA) admitted to collaborating units in the Spanish SEN1500 Network between January 2008 and December 2011. Clinical chorioamnionitis was defined by obstetricians based on clinical findings, and neonatal outcomes were compared between exposed and non-exposed infants by multivariate logistic regression analysis. ***Results:*** During the study period, 11,464 VLBW newborns were admitted to our units and 10,026 were ≤32 weeks' GA. Among them, 8,330 (83.1%) had complete data and were included. Of these, 1,480 (17.8%) were exposed to maternal clinical chorioamnionitis. The incidence was higher at lower GA and, after adjusting for confounding factors, exposed infants had higher risks of early-onset neonatal sepsis (EONS) (10.0 vs. 2.8%; aOR 3.102; 95% CI 2.306–4.173; $p < 0.001$) and necrotizing enterocolitis (NEC) (11.2 vs. 7.7%; aOR 1.300; 95% CI 1.021–1.655; $p < 0.033$), but lower risks of patent ductus arteriosus (PDA) (43.2 vs. 34.9%; aOR 0.831; 95% CI 0.711–0.971; $p < 0.02$) and late-onset bacterial sepsis (LONS) (36.6 vs. 32.5%; aOR 0.849; 95% CI 0.729–0.989; $p < 0.035$). There were no differences in mortality between the groups. ***Conclusions:*** The incidence of maternal clinical chorioamnionitis is inversely related to GA at delivery, and in VLBW infants ≤32 weeks' GA it is associated with higher risks of EONS and NEC, but lower risks of PDA and LONS. We did not found differences in survival.

Introduction

Chorioamnionitis is an inflammatory condition of the intrauterine environment that can lead to a fetal inflammatory response and result in multiorgan injury, preterm premature rupture of membranes, and spontaneous pre-

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Table 1. Baseline perinatal characteristics of preterm infants ≤1,500 g and ≤32 weeks' gestation with and without exposure to maternal clinical chorioamnionitis

Characteristics	Clinical chorioamnionitis (n = 1,480)	Absence of maternal chorioamnionitis (n = 6,850)	Unknown status (n = 1,696)	p value*
GA, weeks	27.1±2.3	28.8±2.3	28.2±2.5	<0.001
Birth weight, g	1,016.0±278.2	1,101.4±267.5	1,063.2±273.9	<0.001
Male gender	54.2	51.6	53.7	0.069
Caesarean delivery	52.2	71.9	70.1	<0.001
Antenatal steroids (at least one dose)	91.5	86.3	80.3	<0.001
Antenatal steroids (complete course)	72.0	65.5	61.3	<0.001
Maternal hypertension (>140/90)	4.3	21.6	17.5	<0.001
Multiple gestation	26.1	36.7	33.3	<0.001
Maternal antibiotics	91.0	41.5	48.2	<0.001
Apgar score at 1 min <3	17.9	13.2	17.7	<0.001
Apgar score at 5 min <7	4.2	2.3	4.4	<0.001
Advanced CPR[1]	50.7	33.8	41.8	<0.001
CRIB	2 (1–6)	1 (1–4)	1 (1–4)	<0.001

Values are mean ± SD, % or median (IQR).* p values for comparison between infants exposed to clinical chorioamnionitis and infants without exposition to maternal chorioamnionitis. [1] Advanced CPR included endotracheal intubation, chest compressions and/or the administration of medications.

term birth, particularly at the earliest gestational age (GA) [1]. Frequently, the inflammation is subclinical, but histological, biochemical, and microbiological findings can be present. However, histological chorioamnionitis is a postnatal diagnosis, routine amniotic fluid cultures may not be appropriate for detecting some pathogens, and the determination of molecular mediators of inflammation may be expensive and time-consuming.

Preterm infants have been considered particularly vulnerable to the effects of chorioamnionitis. Although not consistent in the literature, higher risks of perinatal death, asphyxia, neonatal sepsis, septic shock, pneumonia, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, retinopathy of prematurity (ROP), and developmental delay have been reported [2–5]. After controlling for GA, a recent case-control study could only demonstrate associations of clinical chorioamnionitis with neonatal depression and early sepsis, but not with other prematurity-related complications [6]. It has been suggested that the retrospective design of some studies or the lack of power to detect confounding factors could alter the relationship between clinical chorioamnionitis and neonatal outcomes [7].

Therefore, we conducted a population-based study to determine the incidence of clinical chorioamnionitis in mothers of very-low-birth-weight (VLBW) infants, its relation to GA at birth, and its effects on neonatal morbidity and mortality in these patients.

Patients and Methods

This is a retrospective analysis of prospectively collected data on a cohort of extremely preterm neonates with and without exposure to clinical chorioamnionitis. We collected neonatal and maternal data including all live-born infants ≤1,500 g that were born in or admitted within the first 28 days of life to 53 neonatal intensive care units collaborating in the Spanish SEN1500 Network over a period of 4 years (2008–2011). For the purpose of this research, we excluded infants >32 weeks' GA. The investigation and ethics boards of each hospital had previously approved the protocol. Data were collected using a pre-established form and were submitted electronically using specific common software. The characteristics, quality control, and data confidentiality systems of this database have been described elsewhere [8]. GA was established according to the best available estimation, considering the last maternal menstrual period, obstetrical parameters, and an early gestational ultrasound.

Clinical chorioamnionitis was defined by the presence of maternal fever ≥38°C, after ruling out other causes, in addition to one or more of the following criteria: uterine tenderness, leucocytosis (>15,000 cells/mm^3), maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), or foul-smelling vaginal discharge [9].

Maternal and neonatal demographic data were collected. Neonatal morbidity was compared between exposed and non-exposed infants, including RDS (defined by the presence of respiratory

Table 2. Bivariate comparison of morbidity and mortality between preterm infants ≤1,500 g and ≤32 weeks' gestation who were and were not exposed to maternal clinical chorioamnionitis

Variables	Exposed to clinical chorioamnionitis (n = 1,480)	Absence of maternal chorioamnionitis (n = 6,850)	p value
RDS	69.0	60.2	<0.001
PDA	43.2	34.9	<0.001
EONS	10.0	2.8	<0.001
LONS	36.6	32.5	0.003
NEC	11.2	7.7	<0.001
NEC surgery	8.0	4.7	<0.001
Severe IVH	14.5	8.4	<0.001
PVL	8.4	5.7	<0.001
Oxygen at 28 days	46.5	29.8	<0.001
BPD	23.2	14.9	<0.001
ROP (stage >2)	5.3	3.2	0.001
Mortality	22.6	14.2	<0.001
Survival without major morbidity[1]	42.0	57.1	<0.001

Values are percentages. [1] Major morbidity includes IVH grade 3 or 4, PVL, BPD, NEC, or ROP stage >2.

Table 3. Comparison of outcomes between infants who were and were not exposed to maternal clinical chorioamnionitis after adjusting for GA, birth weight, sex, maternal hypertension, antenatal steroids, maternal antibiotics, multiplicity, type of delivery, necessity of advanced CPR, and CRIB 1

Outcome	aOR	95% CI	p value
RDS	0.861	0.723–1.026	0.095
PDA	0.831	0.711–0.971	0.020
EONS	3.102	2.306–4.173	<0.001
LONS	0.849	0.729–0.989	0.035
NEC	1.300	1.021–1.655	0.033
Severe IVH	0.885	0.694–1.127	0.322
PVL	1.056	0.812–1.373	0.686
BPD	0.949	0.745–1.207	0.668
ROP (stage >2)	0.884	0.592–1.320	0.547
Mortality	0.807	0.647–1.007	0.058
Survival without major morbidity[1]	1.114	0.924–1.344	0.257

[1] Major morbidity includes IVH grade 3 or 4, PVL, BPD, NEC, or ROP stage >2.

symptoms, the need for supplemental oxygen or invasive or non-invasive mechanical ventilation, and a compatible chest X-ray in the first 24 h), patent ductus arteriosus (PDA) (detected by ultrasonography and needing medical or surgical treatment), early-onset neonatal sepsis (EONS) and late-onset bacterial sepsis (LONS) (bacterial infection documented by a positive blood culture in the first 72 h or after, respectively, and with clinical symptoms: apnoea, temperature instability, feeding intolerance, worsening respiratory distress or hemodynamic instability), necrotizing enterocolitis (NEC) (stage ≥2), severe IVH (grade ≥3), PVL (cysts or persistent periventricular echogenicities for more than 14 days), BPD (oxygen dependency at 36 weeks of postmenstrual age), and ROP (stage >2). We also analysed and compared total length of stay, survival, and survival without major morbidity (severe IVH, PVL, BPD, NEC, and/or ROP stage >2).

Data Analysis

Statistical analyses were performed with SPSS-19 software (SPSS, Inc., Chicago, Ill., USA). Continuous variables were expressed as mean and SD or median and interquartile range (IQR), and comparisons between groups were performed with the Student t test or Mann-Whitney U test, as appropriate. Qualitative variables were expressed as proportion (%), and the χ^2 or Fisher's exact tests were used for comparisons. Linear and logistic regression analyses were conducted to estimate the outcomes adjusted for GA, birth weight, maternal hypertension, antenatal steroids, infant sex, multiplicity (2 or more fetuses), type of delivery, necessity of advanced cardiopulmonary resuscitation (CPR), and stability after admission based on the Clinical Risk Index for Babies 1 (CRIB 1) score. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for the outcomes. All the hypotheses were assessed using two-tailed tests, and a p value <0.05 was considered statistically significant.

Results

During the study period 11,464 VLBW newborns were admitted to our units and were assessed for eligibility. Among them, 10,026 were ≤32 weeks' GA and 8,330 (83.1%) with complete data were included. Of these, 1,480 (17.8%) were exposed to maternal clinical chorioamnionitis. The rates of chorioamnionitis were significantly higher at lower GA: 22–26 weeks, 34.2%, 27–30 weeks, 15.9%, and >30 weeks, 5.9% (p < 0.001).

The demographic characteristics and findings at birth of the exposed, non-exposed and 'unknown status' infants are summarized in table 1. Several differences between groups were found and all them were taken into account and corrected for in the logistic regression analysis. Mortality and morbidity were higher among exposed infants in the bivariate comparison (table 2), but after adjusting for potential confounders, only EONS and NEC remained significantly higher (table 3). On the other hand, the aOR for PDA, and LONS were significantly lower among exposed infants.

The length of stay in survivors was longer in the chorioamnionitis group than in the non-exposed group [median (IQR): 62 (44–86.75) vs. 51 (37–70) days, respectively (p < 0.001)], and this difference persisted after adjusting for confounders in the linear regression analysis (p = 0.016). Time to death was similar in both groups [median (IQR): 5 (1–15) vs. 6 (2–17) days (p = 0.583)].

Discussion

The main findings of our study were the inverse correlation of maternal chorioamnionitis with the GA at birth and its association with an increase in the risk of EONS and NEC, and a reduction in the risks of PDA, and LONS. In contrast to other studies, other outcomes (RDS, BPD, IVH, PVL, ROP, etc.) were not associated with clinical chorioamnionitis after adjusting for potential confounders.

The association between chorioamnionitis and respiratory morbidity in the preterm newborn has been extensively studied. While clinical chorioamnionitis has been considered an important risk factor for RDS [10], Watterberg et al. [4] showed that histological chorioamnionitis can stimulate lung maturation, reducing the incidence of acute RDS but increasing lung susceptibility to postnatal damage when exposed to other potential noxious factors. An important issue to consider when referring to this morbidity is the effect of antenatal steroid administration [11] that, in fact, was not widely used when the above-mentioned studies were conducted. Indeed, none of the infants in Watterberg's study received antenatal steroids. In contrast, as a whole, 86.1% of our patients received at least one dose of prenatal steroids, and 65.8% a complete course. Other practices with prognostic implication may also evolve over time or vary among centres. Surfactant was administered to 53.4% of our patients in the delivery room or as soon as possible after admission, and 71.3% received early non-invasive ventilation. Some studies have reported an increased risk of BPD among infants exposed to chorioamnionitis, but many others have reported little or no difference. A maturational effect of prenatal inflammation may be accompanied by structural changes in the lungs [12, 13], and an alteration in the response to exogenous surfactant has also been suggested as a possible cause of prolonged mechanical ventilation in patients with histological evidence of fetal inflammatory response syndrome [14, 15].

The incidence of PDA in relation to exposure to clinical chorioamnionitis is not commonly reported. In a recent large multicentre study, Soraisham et al. [16] found a lower, although not significant, risk of PDA in exposed infants (aOR 0.75; 95% CI 0.56–1.0; p = 0.053). In our study, the risk of PDA was significantly lower among exposed infants after adjusting for confounders (table 3). Both studies are very similar in design, and the greater population size in our study may have influenced the results. The mechanisms underlying the ductal closure are complex [17] and involve vasoactive substances, developmentally regulated potassium and calcium channels, thrombotic sealing by platelets, etc. Although postnatal infection has been clearly related to ductal closure failure [18], we speculate that an intrauterine maturational effect similar to that proposed for the lung could be the reason for this finding.

In their work, Soraisham et al. [16] also found that clinical chorioamnionitis was independently associated with EONS and severe IVH but not with PVL, and that these associations were not the result of increased illness severity. In our study, severe IVH and PVL were more frequent in exposed infants, but the multivariate analysis showed no modifications in the risk. Again, the results in the literature are controversial [10, 19, 20]. However, the meta-analysis by Wu and Colford [21] showed that clinical chorioamnionitis increased the risk of cystic PVL and cerebral palsy. Unfortunately, the variability in the criteria used to define chorioamnionitis and the lack of a normal control group make it difficult to compare outcomes. In addition, most studies included only cases of cystic PVL, which is now estimated to constitute less than 10% of all cases of white matter damage. Cerebral non-cystic white matter injury has been related to perinatal infection, particularly maternal fever and infant sepsis [22]. The role of proven sepsis, independent of other risk factors, in the development of neurological impairment in extremely preterm infants has also been shown by others [23].

An almost universal finding in most studies is the increased risk of EONS, both in clinical and histological chorioamnionitis [6, 10, 16, 24–26]. In our study the incidence of EONS was significantly higher among infants exposed to maternal clinical chorioamnionitis, and this association persisted after adjusting for GA, birth weight, and all other confounders. An interesting finding in our study was the significantly reduced risk of LONS. This apparently protective effect against LONS has been recently reported by Strunk et al. [26] in infants exposed to histological chorioamnionitis. A possible explanation could be that EONS is generally caused by virulent bacteria that are vertically transmitted from the mother. However, less virulent microorganisms are frequently involved in chorioamnionitis and cause inflammation of placental tissues but not acute disease in the newborn. This exposure may stimulate the maturation of the neonatal immune system, but the exact mechanism is not completely understood [26].

We also found a significant increase in the risk of NEC among neonates exposed to clinical chorioamnionitis. As highlighted in a recent systematic review and meta-analysis [27], clinical chorioamnionitis is significantly associated with NEC (OR 1.24; 95% CI 1.01–1.52; p = 0.04), as is histological chorioamnionitis with fetal involvement (OR 3.29; 95% CI 1.87–5.78; p < 0.001). Both NEC and

LONS have been associated with white matter damage and adverse neurodevelopment in preterm infants [28].

A limitation of our study is the lack of histopathology of the placenta and the umbilical cord. A recent study by Pappas et al. [29] showed that 2.7% of cases diagnosed with clinical chorioamnionitis had a normal placental histology. Nevertheless, clinical chorioamnionitis, once other causes of maternal fever have been excluded, may represent the most severe cases of fetal-placental inflammation. In addition, clinical diagnosis is faster and easier and could be useful in guiding clinical decision-making from a practical perspective. Recently, Been et al. [30] developed a clinical prediction rule based on clinical variables available at birth to predict histological chorioamnionitis and histological chorioamnionitis with fetal involvement in singleton preterm newborns ≤32 weeks' GA. Although not applicable to multiplets, more mature newborns, or when the diagnostic criteria for histological chorioamnionitis used are different, these rules showed good positive and negative predictive values. The authors concluded that further studies should evaluate their clinical value to guide early treatment individualisation.

Another potential limitation of this study is its character of nationwide registry with many different participating investigators that could lead to some inconsistencies in the data collection. However, operational definitions were clearly established and agreed upon at previous meetings between all the principal investigators from each centre. On the other hand, the multicentre approach of the study could make the results more generalizable. Finally, in 1,696 patients (16.9%) the exposure to clinical chorioamnionitis was missed (unknown status). This could have contributed some bias to our results. Nevertheless, this is a relatively low proportion and their demographic characteristics (table 1) suggest that this group is composed of a random mixture of exposed and unexposed patients.

The principal strength of our study is its large sample size and its population-based nature. The exposure of our patients to antenatal steroids was greater than 80%, and they were managed in a standard manner by the perinatal teams of the participating units. The diagnosis of clinical chorioamnionitis, as carried out in this work, was quick and not expensive, and could be useful regarding clinical decision-making. Some fetuses could benefit from early delivery to avoid continuing intrauterine inflammation, taking into account its potential implications in the long run [21, 31]. Some newborns could also benefit from a more appropriate type and duration of postnatal antibiotherapy.

In conclusion, our results support previous evidence indicating that the incidence of maternal clinical chorioamnionitis is inversely related to GA. VLBW infants ≤32 weeks' GA born to mothers with this condition have a lower risk of PDA, but the risk of RDS and BPD are not modified. In addition, exposure to clinical chorioamnionitis confers to the newborn higher risks of EONS and NEC, but it seems to be associated with a significantly reduced risk of LONS in this population. The exact mechanisms of these effects deserve further investigation.

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Erratum

The following Appendix should be included in the paper entitled 'Outcomes of very-low-birth-weight infants exposed to maternal clinical chorioamnionitis: a multicentre study' by García-Muñoz Rodrigo et al. [Neonatology 2014;106:229–234, DOI: 10.1159/000363127].

Appendix

The hospitals, investigators and coordinators of the Spanish Neonatal Network SEN1500 are as follows:

Complejo Hospitalario Albacete (Andrés Martínez Gutiérrez); Complexo Hospitalario A Marcide (José Luaces González); Corporació Parc Taulí (Juan Badia); Fundación Hospital De Alcorcón (Ana Martín Ancel); Hospital Basurto (Gabriel Saitua Iturriaga); Hospital Bierzo (María Teresa González Martínez); Hospital Cabueñes (Adela Rodríguez Fernández); Hospital Cantabria (Javier Gómez-Ullate Vergara); Hospital Carlos Haya (Tomás Sánchez Tamayo); Hospital Central Asturias (C. Moro Bayón); Hospital Clínic Barcelona (Josep Figuera Aloy); Hospital Clínico San Carlos (Tamara Carrizosa Molina); Hospital Cruces (Carolina de Castro Laíz); Hospital de Granollers (Israel Anquela Sanz); Hospital de la Santa Creu i Sant Pau (Gemma Ginovart Galiana); Hospital de la Zarzuela (Marisa López Gómez); Hospital Donosita (Luis Paisan Grisolía); Hospital Elche (Josep Mut Buigues); Hospital Germans Trias i Pujol (Antonio Natal Pujol); Hospital Getafe (Marta Muro Brussi); Hospital Infanta Margarita (José María Barcía Ruiz); Hospital Trueta (Alberto Trujillo); Hospital Jerez (Joaquín Ortiz Tardío); Hospital Juan Canalejo (José Luis Fernández Trisac); Hospital Juan Ramón Jiménez (José Ángel Morilla Sánchez); Hospital Juan XXIII (Juan Manuel Carretero Bellón); Hospital León (Emilio Álvaro Iglesias); Hospital Miguel Server (José Julián Beltrán Crouset); Hospital Montepríncipe (Marta García San Miguel); Hospital Móstoles (Lorenzo Sánchez de León); Hospital Mutua de Terrassa (Ángel Moral García); Hospital Nuestra Sra. de Sonsoles (Antonio Martín Sanz, Manuel Marrero); Hospital San Juan de Deu (Martín Iriondo Sanz); Hospital San Pedro (Fermín Cucalón Manzanos); Hospital San Pedro de Alcántara (Ana Barrio Sacristán); Hospital Severo Ochoa (María José Santos Muñoz); Hospital Son Dureta (Pere-Ramón Balliu Badía); Hospital Txagorritxu (María Mercedes Martínez Ayucar); Hospital Universitario Arnau de Vilanova (Eduard Solé Mir); Hospital Vall Hebron (Anna Fina Martí); Hospital Valme (Antonio Gutiérrez Benjumea); Hospital Virgen de la Concha (Víctor Marugán Isabel); Hospital Virgen de la Luz (Elisa Cueto Calvo); Hospital Virgen de la Macarena (Mercedes Granero Asencio); Hospital Virgen de la Salud (Alicia de Ureta Huertas); Hospital Virgen de las Nieves (Luis Fidel Moltó Ripio); Hospital Xeral Vigo (Socorro Ocampo Cardalda); Hospital Universitario de Valencia (Javier Estañ Capell); Hospital Universitario de Zaragoza (Purificación Ventura Faci); Hospital Universitario Santiago (José María Fraga); Hospital General Castellón (Ramón Aguilera Olmos); Hospital General Segovia (Miryam Hortelano); Hospital General Yagüe (Bruno Alonso Álvarez); Hospital General Universitario Alicante (Manuela López Azorín); Hospital Universitario Gregorio Marañón (Amparo Rodríguez Herreras); Hospital Universitario La Paz (Jesús Pérez Rodríguez); Hospital Materno Infantil de Canarias (Fermín García-Muñoz Rodrigo); Hospital Universitario Canarias (Pedro Amadeo Fuster Jorge); Hospital Universitario de San Cecilio (Eduardo Narbona); Hospital Universitario La Fe (Vicente Roqués); Hospital Universitario Reina Sofía (Juana María Guzmán Cabañas); Hospital Universitario Río Hortera (Carmen González Armengol); Hospital Universitario Salamanca (Pilar García González); Hospital Universitario San Juan (Javier Gonzalez de Dios); Hospital Universitario Valladolid (José Luis Fernández Calvo); Hospital Universitario Virgen del Rocío (Carmen Macías Díaz); Institut Dexeus (Roser Porta); Scias-Hospital Barcelona (Xavier Demestre).