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CLINICAL ARTICLE

Obstetrics

Effect of acute histologic chorioamnionitis on bronchopulmonary dysplasia and mortality rate among extremely low gestational age neonates: A retrospective case–control study

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Abstract

Objective: To evaluate whether acute histologic chorioamnionitis (HCA) diagnosed in the placenta may be associated with an increased occurrence of bronchopulmonary dysplasia (BPD) or death among extremely low gestational age neonates (ELGAN).

Methods: This Italian single-center case–control retrospective study involved ELGAN admitted to the neonatal intensive care unit between January 2019 and June 2022. Infants born from pregnant women with acute and severe HCA, identified as stage ≥2 and grade 2 HCA, (HCA-infants) were compared with infants of pregnant women without chorioamnionitis or with stage 1, grade 1 chorioamnionitis (no-HCA-infants).

Results: Among 101 eligible ELGAN, 63 infants had complete clinical and histologic data relevant to the study: thirty infants were included in the HCA-infants group and 33 in the no-HCA-infants group. Neonatal and maternal demographic and clinical characteristics were similar between the two groups. Infants born from mothers with acute and severe HCA had significantly higher occurrence of composite BPD or death (18 [60%] vs. 9 [27%]; $P=0.012$), as well as higher incidence of severe forms of BPD (6 [30%] vs. 2 [6%]; $P=0.045$). In multiple logistic regression analysis, after adjustment for confounding covariates, HCA was an independent risk factor for BPD or death (OR, 4.49; 95% CI: 1.47–13.71).

Conclusions: This is the first study showing that in utero exposure to acute and severe HCA is an independent risk factor for the occurrence of composite BPD or death among ELGAN.

KEYWORDS

bronchopulmonary dysplasia, extremely low gestational age, extremely premature, histologic chorioamnionitis, infant, premature birth

1 | INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most common complications of prematurity, affecting up to 50%–60% of extremely low gestational age neonates (ELGAN).[1]

Though advances in neonatal intensive care have led to improved survival, the rates of BPD have remained the same or even increased among ELGAN.[1–3]

BPD is not just a lung disease, but a systemic condition with sequelae that can undermine health and quality of life in a later age. Indeed, while pulmonary disease improves with the child development, persistent pulmonary dysfunctions can develop also in young adults after BPD.[4] For this reason, the prevention of BPD is a challenging priority for extremely preterm infants.

Evidence shows that BPD occurs secondary to genetic-environmental interactions in an immature lung.[5] It is important for prevention to identify manageable risk factors. Among the risk factors involved in the pathogenesis of BPD, exposure to inflammation plays a significant role.[6] The most common inflammation source that affects preterm infants is the one resulting from chorioamnionitis, where inflammation can affect almost every organ of the developing fetus, leading to a real multiorgan disease.[7]

In this study, we hypothesized that acute histologic chorioamnionitis (HCA) diagnosed in the placenta may be associated with an increased occurrence of BPD and death among ELGAN.

2 | MATERIALS AND METHODS

2.1 | Design of the study, setting, and patients

This was a retrospective case–control study performed in infants born at less than 28^{+0} weeks of gestational age (GA), and admitted to the neonatal intensive care unit of Fondazione Policlinico Universitario Agostino Gemelli, IRCCS in Rome – Italy (FPG), between January 2019 and June 2022. Infants who died in the delivery room or within the first 24 h of life, those born elsewhere or transferred to another hospital before completing 36 weeks of postmenstrual age (PMA), and those with congenital malformations, metabolic disorders, or with incomplete data relevant to the present study were excluded.

Infants born from pregnant women with acute and severe HCA, identified as stage ≥2 and grade 2 HCA (HCA-infants) were compared with infants of pregnant women without chorioamnionitis or with stage 1, grade 1 chorioamnionitis (no-HCA-infants). Staging and grading of the HCA were based on the Amsterdam Placental Workshop Group Consensus Statement on Sampling and Definitions of Placental Lesions.[8]

The study was carried out in compliance with the Declaration of Helsinki and approved by the Ethics Committee of FPG (in the context of the protocol number ID 3244). Written informed consent was obtained from parents for any clinical research purpose about the collected clinical data.

2.2 | Primary and secondary outcomes

The primary outcome was the incidence of the composite of BPD or death. The secondary outcomes were the occurrence of moderate BPD, severe BPD, and death. Moderate BPD was defined as oxygen supplementation for at least 28 days and persistent need for oxygen ($FiO_2 < 30\%$) at 36 weeks' PMA. Severe BPD was defined as oxygen supplementation for at least 28 days and persistent need for oxygen ($FiO_2 \geq 30\%$), ventilatory support (mechanical ventilation and/or continuous positive airway pressure) at 36 weeks' PMA.[9]

2.3 | Data collection

Maternal characteristics data comprised: age, parity, mode of delivery, multiple pregnancy, antenatal corticosteroids, fetal Doppler flow velocimetry abnormalities (intended as absent or reversed end diastolic flow velocity), preterm premature rupture of the membranes (pPROM), smoking habit, body mass index, obstetrical diseases - such as gestational and pregestational diabetes, pregestational hypertension and pre-eclampsia-, and histologic diagnosis of chorioamnionitis in the placenta. Microbiologic culture results of vaginal, rectal swabs and the placenta were recorded.

Neonatal characteristics data comprised: GA, birth weight (BW), gender, 1 and 5-min Apgar score, delivery room intubation, surfactant administration. The occurrence of death, moderate and severe BPD,[9] grades 3–4 intraventricular hemorrhage (IVH),[10] hemodynamically significant patent ductus arteriosus (hsPDA) requiring treatment, persistent pulmonary hypertension (PPH) was recorded. The occurrence of early onset sepsis (EOS), occurring before 72 h of life, and late onset sepsis (LOS), occurring at or after 72 h of life, was registered. Confirmed EOS and LOS was defined by a positive blood culture, while clinical EOS and LOS was defined by suggestive clinical and laboratory findings leading to treatment with antibiotics for at least 7 days despite absence of a positive blood culture. Duration of mechanical ventilation and oxygen therapy were also recorded. All data were collected from electronic clinical records.

The placentas post-delivery were sent to the laboratory for histopathologic examination and culture. The methodology of histopathologic and microbiologic examinations is provided in the supplementary material.

2.4 | Sample size and statistical analysis

The sample size was calculated based on our observational data showing that, among the ELGAN born from mothers without acute severe HCA, the incidence of the composite of individual BPD or death was ~26%. Sample size calculation demonstrated that at least 30 patients for each group were needed to detect an increased

incidence of BPD or death to 60% with a power of 80% and an α error of 0.05.[11]

HCA infants were matched on a 1:1 ratio with those without chorioamnionitis or with stage 1, grade 1 chorioamnionitis (no-HCA infants). We matched using IBM Statistics SPSS version 25.0 (IBM Software, Chicago, Illinois, USA, 2016) and matchings were based on GA (±6 days) and BW (±100 g).

Categorical data are expressed as number and percentage and numerical data are reported as mean and standard deviation or median and interquartile range. A Shapiro–Wilk test was used to verify normal distribution of continuous data. Categorical data were compared using Chi-square test or Fisher exact test; numerical data were compared using the student *t*-test for independent samples or Mann Whitney test. We performed a multiple logistic regression analysis with HCA and GA as the independent variables, and composite outcome of BPD and death as dependent variable, to calculate the odds ratio. Statistical analysis was performed using Statistical Package for Social Science (SPSS®, IBM®) version 25. A *P* value less than 0.05 was considered statistically significant.

3 | RESULTS

A total of 101 eligible ELGAN were born in the FPG between January 2019 and June 2022.

A total of 13 infants were excluded because they died in the delivery room or within the first 24 h of life, 11 newborns were excluded because they were born elsewhere, two because they were transferred to another hospital before completing the 36 weeks of PMA, and 12 because of incomplete data.

A total of 63 infants (62%) had complete clinical and histological data relevant to the study: thirty infants met the criteria for inclusion in the HCA-infants group and 33 in the no-HCA-infants group.

Neonatal demographic and clinical characteristics were similar between the groups (Table 1).

Given the presence of twin pregnancies, HCA-Infants were born to 26 mothers while no-HCA-Infants were born to 28 mothers; no statistical differences between the demographic and clinical characteristics of the two groups of mothers were observed (Table 2).

TABLE 1 Neonatal demographic and clinical characteristics.

	HCA infants (*N* = 30)	No-HCA infants (*N* = 33)	*P* value
Gestational age, weeks	26.3 ± 1.2	26.3 ± 1.1	0.918
Birth weight, grams	0.83 ± 0.19	0.83 ± 0.20	0.964
Male gender, *n*	17 (56.7)	19 (57.6)	1
Preterm premature rupture of membranes >18 h, *n*	15 (50)	4 (12.1)	0.002
Preterm premature rupture of membranes, hours	17 (1–510)	0 (1–5)	0.175
Clinical chorioamnionitis, *n*	6 (20)	6 (18.2)	1
Small for gestational age, *n*	4 (13.3)	4 (12.1)	1
Cesarean delivery, *n*	20 (66.6)	23 (69.7)	0.780
Fetal flow velocimetry abnormalities,[a] *n*	5 (16.7)	11 (33.3)	0.129
1-min Apgar score	5 (4–6)	5 (3–7)	0.922
5-min Apgar score	8 (7–8)	8 (6–8)	0.865
Delivery room intubation, *n*	15 (50.0)	12 (36.4)	0.316
Surfactant administration, *n*	23 (76.7)	26 (78.8)	1
3–4 grade intraventricular hemorrhage, *n*	5 (16.7)	9 (27.3)	0.373
Confirmed late onset sepsis, *n*	3 (10)	4 (12.1)	0.922
Gram-positive bacteria sepsis, *n*	2 (6.7)	4 (12.1)	0.674
Gram-negative bacteria sepsis, *n*	1 (3.3)	0	0.482w
Early onset sepsis, *n*	0	1 (3.0)	1
Clinical late onset sepsis, *n*	17 (56.7)	13 (39.4)	0.170
Late onset sepsis, *n* > 2	6 (20.0)	7 (21.2)	0.905
Hemodynamically significant patent ductus arteriosus, *n*	14 (46.7)	15 (45.5)	1
Persistent pulmonary hypertension	7 (23.3)	9 (27.3)	0.720
Mechanical ventilation duration, days[b]	3 (0–11)	5 (0–19)	0.231
Mechanical ventilation at 36 weeks of PMA	2 (6.7)	0	0.223
Oxygen therapy duration, days[b]	36 (7–83)	21 (8–50)	0.314

Note: Data are expressed as number (percentage), mean (standard deviation), median (interquartile range).

Abbreviations: HCA, histologic chorioamnionitis; PMA, postmenstrual age.

[a]Fetal flow velocimetry abnormalities include absent or reversed end-diastolic flow in umbilical artery.

[b]Data are referred to survivor infants only.

TABLE 2 Characteristics of mothers with and without histologic chorioamnionitis.

	HCA mothers ($N=26$)	No-HCA mothers ($N=28$)	*P* value
Age, years	33.7 ± 5.3	34.8 ± 5.9	0.483
Antenatal steroids: 2 doses	17 (65.3)	16 (57.1)	0.786
Antenatal steroids: 1 dose	8 (30.7)	7 (25.0)	1
Primiparity, *n*	6 (23.1)	10 (35.7)	0.479
Multiple pregnancy, *n*	4 (15.4)	5 (17.8)	1
Smoking habit, *n*	1 (3.8)	0	0.482
Medical assisted procreation, *n*	0	5 (17.9)	0.052
Body mass index, %	22 (20–25)	26 (23–29.5)	0.040
Gestational diabetes	0	0	–
Pregestational diabetes	0	0	–
Pre-eclampsia	3 (11.5)	1 (3.6)	0.342
Pregestational hypertension	0	3 (10.7)	0.237
Hypothyroidism	2 (7.7)	2 (7.1)	1

Note: Data are expressed as number (percentage), mean (standard deviation), median (interquartile range).
Abbreviation: HCA, histologic chorioamnionitis.

TABLE 3 Primary and secondary outcomes.

	HCA infants ($N=30$)	No-HCA infants ($N=33$)	*P* value
Bronchopulmonary dysplasia or death	18 (60)	9 (27)	0.012
Moderate bronchopulmonary dysplasia	2 (10)	5 (16)	0.690
Severe bronchopulmonary dysplasia	6 (30)	2 (6)	0.045
Death	10 (33)	2 (6)	0.009

Note: Data are expressed as number (percentage).
Abbreviation: HCA, histologic chorioamnionitis.

Infants born from mothers with acute and severe HCA had significantly higher occurrence of composite BPD or death, as well as higher incidence of severe forms of BPD (Table 3).

In multiple logistic regression analysis, after adjustment for confounding covariates, we found that HCA was an independent risk factor for BPD or death (Table 4). Meanwhile, GA was not associated with an increased risk of developing BPD, although this result was close to statistical significance.

Gram-negative microorganisms were more represented in the cultures of mothers with HCA, when compared to those of mothers without HCA, and the *E. coli* infection rate was the highest identified in 11 (42%) mothers with HCA (Table 5).

4 | DISCUSSION

The present study has shown that ELGAN exposed to acute and severe HCA in utero have a significantly higher incidence of composite BPD or death compared to controls. In addition, they had a significantly higher occurrence of the severe forms of BPD.

In our study population, perinatal factors potentially leading to the development of BPD such as fetal flow velocimetry abnormalities, GA, need for intubation in the delivery room, need for surfactant administration indicating respiratory distress syndrome (RDS) presence were equally distributed between the two groups. This strongly suggests that the degree of severity of HCA may influence the occurrence of severe BPD or death. Indeed, multiple logistic regression analysis found that HCA was an independent risk factor increasing the occurrence of BPD or death by more than four-fold.

Our results do not support the conclusions reported by Liu et al., who observed a protective effect of mild HCA against RDS, and no correlation with BPD after multivariate adjustment.[12] The inconsistency between ours and their findings could be caused by two factors. First, our study population included only extremely preterm infants, <28 weeks of GA, who are more fragile than the very low birthweight infants studied by Liu et al. Second, Liu et al. also included grade 1 HCA in the group of infants from women with HCA, perhaps mitigating the severity of inflammation that chorioamnionitis exerted on the lungs. To exclude this possibility, we chose to not include in our HCA group infants of women with only grade 1, stage 1 HCA, because at this stage, the presence of protective neutrophils in the subcortical intervillous space or below the chorionic layer is synonymous with sub chorioamnionitis and not with acute chorioamnionitis.[8] Consequently, we included infants by mothers with grade 1, stage 1 HCA, in the No-HCA Infants group.

TABLE 4 Multiple logistic regression analysis for BPD moderate/severe or death.

	OR for BPD moderate/severe or death	CI 95%	*P* value
Histological chorioamnionitis	4.49	1.47–13.71	0.008
Gestational age	0.62	0.38–1.00	0.052

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval.

TABLE 5 Frequency of isolated microorganisms from vaginal swabs and/or placenta.

	HCA mothers (*N* = 26)	No-HCA mothers (*N* = 28)	*P* value
Isolated microorganisms			
Gram-negative	16	3	<0.001
Escherichia coli	11	1	0.001
Klebsiella pneumoniae	3	0	0.105
Others[a]	2	2	1
Gram-positive	6	3	0.286
Listeria monocytogenes	0	1	1
Staphylococcus aureus	1	0	0.482
Streptococcus agalactiae	5	2	0.243
Anaerobes	4	5	1
Bacteroides fragilis	2	0	0.227
Bacteroides vulgatus	1	0	0.482
Fusobacterium nucleatum	1	0	0.482
Others[b]	0	5	0.052
Mycoplasmas	4	1	0.184
Ureaplasma parvum	4	1	0.184

Abbreviation: HCA, histologic chorioamnionitis.

[a]Includes *Klebsiella aerogenes* (*n* = 2), *Klebsiella oxytoca* (*n* = 1), *Proteus mirabilis* (*n* = 1).

[b]Includes *Finegoldia magna* (*n* = 1), *Peptostreptococcus anaerobius* (*n* = 1), *Prevotella bivia* (*n* = 2), *Veilonella parvula* (*n* = 1).

The potential adverse effect of HCA on BPD development in preterm neonates remains unsettled.

Watterberg et al. first reported an association between chorioamnionitis and both an increased risk of chronic lung disease and a decreased risk of RDS, leading to the hypothesis that chorioamnionitis exposure accelerates functional lung maturation but increases the susceptibility of the immature lung to postnatal damage.[13]

A meta-analysis by Villamor-Martinez et al., including more than 240 000 very low birthweight preterm infants, confirmed that exposure to chorioamnionitis was associated with a higher risk of developing BPD, but this association may be modulated by the GA and the presence of RDS.[14] Conversely, a previous large epidemiologic study found that the risk of moderate or severe BPD and the combined outcome of death or BPD was lower for very preterm infants with HCA than in very preterm infants without HCA.[15] These conflicting results could be due to the heterogeneity of the available studies, regarding both the definition of chorioamnionitis—clinical or histologic—and the degree of severity of the HCA present.

Acute chorioamnionitis is a maternal inflammatory response caused by ascending microorganisms (bacteria, virus, parasites) reaching through the cervix into the amniotic cavity causing an intra-amniotic infection. In delivery at 21–24 weeks of gestation, chorioamnionitis is present in 94% of cases.[16] However, the rates of placental infection are lower. Diagnosis of acute chorioamnionitis is based on clinical signs, such as maternal fever, fetal tachycardia, uterine tenderness, contractions, elevated white count, and ruptured membranes with foul-smelling amniotic fluid.[16]

Triple I criteria (intrauterine inflammation or infection or both) are a recently proposed method to diagnose chorioamnionitis.[17] The clinical signs of intraamniotic infection are not as specific as histologic examination of the placenta. HCA has a better predictive value for intra-amniotic infection than clinical signs as it has a negative predictive value of 97% and a positive predictive value of 79%, compared to amniotic fluid cultures.[18]

From a global perspective, the rate of preterm birth is highest in countries defined as low middle income countries, where the access for newborn care is highly limited.[19] Therefore, it is encouraging to note, based on our findings, that when only a grade 1, stage 1 HCA is present, the risk of later BPD development remains low. We recently reported FIGO good clinical practice for diagnosing and treatment of preterm labor, pPROM, and chorioamnionitis, in order to provide up-to-date rapid triage preparation for labor practical diagnostic tools, implementable both at primary sites and in hospital settings without access to cultures or placental histology.[20] We also provided FIGO

good clinical practice updated guidelines of rapid newborn triage to diagnose and manage low risk on site, while those at risk are managed on site or transferred.[21] Such recommendations could minimize severe chorioamnionitis and improve mother-newborn dyad outcome.

It has been suggested that a greater severity of HCA may lead to worse neonatal outcomes; however, no clear evidence has yet been found to support an increase in BPD and morbidity, nor a correlation with the stage or grade of HCA, while an inverse relationship was observed between the incidence of neonatal morbidity and the GA.[22,23] To our knowledge, the present study is the first to identify acute and severe HCA as an independent risk factor for mortality and BPD among ELGAN.

Postnatal infections, such as sepsis and pneumonia, are also risk conditions for BPD. In both pre- and postnatal infections, lung damage is likely mediated by inflammatory cytokines. These cytokines might be produced by inflammatory cells present in the lung or airways or enter the lung via pulmonary circulation. Additionally, lung tissue injury caused by barotrauma and oxygen toxicity leads to the release of inflammatory mediators associated with the development of BPD. Thus, mechanical ventilation contributes to increase pulmonary inflammation already induced by pre- and postnatal infection.[24–26]

Van Marter et al. found that chorioamnionitis was associated with an increased risk of chronic lung disease if mechanical ventilation was sustained for more than 7 days or if postnatal sepsis developed in the preterm infants[12] In our experience, both incidence of EOS and LOS and duration of mechanical ventilation were not different in HCA and No-HCA patients, as a consequence of our internal protocols aimed at extubating all infants already within the first week of life. This corroborates our finding of HCA being an independent risk factor for the development of BPD.

E. coli bacteria infection was significantly more frequent among cultures of women with HCA. This finding is in agreement with recent observations showing an increase in *E. coli* infections among very low birth weight infants and among late preterm infants.[27–29] Such an observation is important since this bacterium is part of the endogenous gut flora, raising awareness of the need for improved local hygiene to prevent such ascending infection, especially when pPROM is suspected or confirmed.

This study had some strengths but also some limitations. The strengths lie in the uniformity of the protocols for the care of premature infants included in the study, the homogeneity of the characteristics of the two study populations and the possibility of defining chorioamnionitis based on strict histologic criteria. The limitations lie in the retrospective nature of the study and its potential selection bias, which could have prevented the evaluation of other variables possibly related to the development of BPD.

5 | CONCLUSIONS

In utero exposure to acute and severe HCA is an independent risk factor for the occurrence of composite BPD or death among ELGAN. We believe that further research is needed to find new therapeutic strategies aimed at mitigating inflammation resulting from HCA as a preventive weapon against BPD.

AUTHOR CONTRIBUTIONS

Giovanni Vento, Simonetta Costa, and Marco De Santis contributed to the conception and design of the study, and to the interpretation of data for the study. Simona Fattore, Mariarita Trapani, and Milena Tana contributed to the acquisition and to the analysis of data. Simonetta Costa drafted the manuscript. Vincenzo Arena performed the histologic examinations. Teresa Spanu and Maurizio Sanguinetti performed microbiologic examinations. Giovanni Vento, Anronio Lanzone, and Eytan R. Barnea critically reviewed the manuscript for important intellectual content.

All authors approved the final version to be published and agreed to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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