The Association of Histological Chorioamnionitis and Antenatal Steroids on Neonatal Outcome in Preterm Infants Born at Less than Thirty-Four Weeks' Gestation

Hye Mi Ahn^a Eun Ae Park^a Su Jin Cho^a Young-Ju Kim^b Hye-Sook Park^c

Departments of ^aPediatrics, ^bObstetrics and Gynecology and ^cPreventive Medicine, School of Medicine, Ewha Womans University, Seoul, Korea

Key Words

Chorioamnionitis · Antenatal steroids · Preterm infants

Abstract

Background: Despite continuous research on the prevention of preterm labor, preterm delivery still occurs often. Different neonatal outcomes in association with chorioamnionitis might occur with the introduction of antenatal steroids.

Objective: The purpose of this study was to determine the effect of chorioamnionitis on the outcome of preterm infants and the association of antenatal steroids in the presence of histological chorioamnionitis (HC). **Methods:** Two hundred and fifty-seven infants born at <34 weeks and admitted to Ewha Womans University Hospital from 2005 to 2010 were enrolled. They were divided into 2 groups, one with HC (n = 89) and the other without HC (n = 168). The clinical characteristics and outcomes of the preterm infants including sepsis, respiratory distress syndrome, intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD) were analyzed. **Results:** HC was associated with IVH (p = 0.019) and early-onset sepsis (p = 0.038). In the HC group, the infants exposed to antenatal steroids developed BPD less than those without steroid exposure. The duration of mechanical ventilation was significantly decreased in the group with antenatal steroids. **Conclusion:** HC increased the incidence of early-onset sepsis and IVH in preterm infants of

less than 34 weeks' gestation with a high odds ratio of 9.54. In the presence of HC, antenatal steroids significantly decreased the incidence of BPD. Copyright © 2012 S. Karger AG, Basel

Introduction

Despite continuous research on the prevention of preterm labor, preterm delivery continues to occur frequently. Chorioamnionitis is known as one of the important causes of preterm birth and the incidence in preterm infants increases with decreasing gestational age [1]. The pathogenesis of chorioamnionitis is initiated by the passage of infectious organisms to the chorioamnion or umbilical cord of the placenta and this occurs most commonly by retrograde or ascending infection from the lower genital tract [2]. Although there is a significant overlap between clinical and histological chorioamnionitis (HC), the latter is a more common diagnosis based on pathological findings upon microscopic examination of the placenta encompassing clinically unapparent chorioamnionitis and clinical chorioamnionitis [3]. It is generally felt that a histological definition of intrauterine inflammation more closely reflects antenatal inflammatory exposure than the clinical definition [4].

Intrauterine exposure to infection is known to induce a fetal inflammatory response by the release of a combination of proinflammatory and inhibitory cytokines which is associated with an increased incidence of lung and brain injury. Regarding the neurological outcome, a meta-analysis of observational studies revealed a significant association between chorioamnionitis, cystic periventricular leukomalacia (PVL) and cerebral palsy [5]. However, for pulmonary outcome, fetal exposure to inflammation can have both detrimental or beneficial effects on the preterm lung. Watterberg et al. [6] were the first to report a decrease in the incidence of respiratory distress syndrome, while the incidence of chronic lung injury was increased in infants with chorioamnionitis. Some studies have shown an increased risk of bronchopulmonary dysplasia (BPD) in infants with chorioamnionitis [7] and others show no change [1]. More recently, many do not show a greater incidence of BPD; Been and Zimmermann [8] suggest that this may be attributed to the increased use of antenatal steroids over the last 15 years.

BPD in infants with a very low birth weight is the net result of lung injury, repair and disrupted development that should be viewed as a sequence of adverse events of 'hits' [9]. Among the possible events, lung maturation is inducible with antenatal steroid therapy, which decreases the risk of severe lung immaturity [10]. To induce lung maturation, treatment with antenatal steroids has become standard, but there is a lack of evidence or knowledge on their administration and the neonatal outcome for infants with chorioamnionitis.

The aim of our study was to examine the effects of chorioamnionitis on neonatal morbidity in a prospective cohort of preterm infants, focusing, in particular, on the combined effects of antenatal steroid therapy and chorioamnionitis.

Materials and Methods

Subjects

This study was a prospective, observational study. The study cohort included all infants with a birth gestational age of <34 weeks who were admitted to Ewha Woman's University Hospital between January 1, 2005 and December 31, 2010. Antenatal, perinatal and neonatal data were prospectively stored in a database. The study was carried out with the approval of the ethics committee of Ewha Womans University Hospital and written informed consent was obtained from the parents of all subjects at mid-pregnancy. Exclusion criteria comprised infants with major congenital anomalies and outborn infants.

The placentas of the infants were routinely sent for histological examination. The infants were divided into 2 groups: 1 with HC

(n = 89) and the other without HC (n = 168) based on the pathological findings of the placenta. Clinical characteristics and outcomes including sepsis, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), BPD and intrahepatic cholestasis (IHC) of both groups were analyzed.

We used the following clinical definitions. Small-for-gestational-age (SGA) was defined as a birth weight less than the 10th percentile for gestational age. The fetal-infant growth chart for preterm infants by Fenton [11] was used for the classification of SGA. Early-onset sepsis was defined as a positive blood culture occurring within the first 72 h. Late-onset sepsis was defined as positive blood culture within 4–30 days of life. IVH was defined according to the IVH grading by Papile et al. [12] and only severe IVH (grades 3 and 4) was included in this study. PVL was defined according to Volpe [13]. RDS was diagnosed in infants with respiratory distress, an increased oxygen requirement and a radiological finding consistent with RDS. National Institute of Child and Human Development criteria were used to define BPD, and moderate and severe BPD were included in this study [14]. IHC was defined when conjugated bilirubin exceeded 2.0 mg/dl. Significant necrotizing enterocolitis (NEC) was defined as stage 2 or higher according to modified Bell's criteria [15]. Patent ductus arteriosus (PDA) was diagnosed by echocardiography and medical treatment or surgical ligation were performed when necessary. Antenatal steroid exposure was defined as maternal receipt of dexamethasone during the admission for delivery. A complete course of dexamethasone was defined as four 5-milligram intramuscular doses given at 12-hour intervals. The study included infants who received incomplete courses.

Histopathology

Placentas and membranes were fixed in formalin and embedded in paraffin immediately after delivery. Sampling was performed according to a standard protocol; to prevent bias from interexaminer variation, samples were examined by a single pathologist blinded for clinical information. Cases were classified as chorioamnionitis when there was acute inflammation with polymorphonuclear leukocyte infiltration into the chorionic-plate fibrin, fibrous chorion or amnion. Chorioamnionitis was defined as HC when it was grade 2 or more according to the grading system suggested by Salafia et al. [16].

Statistical Analyses

Statistical analyses were performed with the SPSS version 18.0 for Windows. Categorical variables were analyzed with the χ^2 test and the Fisher exact test. Continuous variables were analyzed by the Student t test or the Mann-Whitney U test. Multiple logistic (or linear) regression models adjusting for gestational age were performed. $p < 0.05$ was considered statistically significant. Odds ratios (OR) and 95% confidence intervals (CI) are reported.

Results

Clinical Characteristics of Study Subjects

Two hundred and fifty-seven preterm infants were included in the study, 89 of whom had HC. Table 1 shows the demographic characteristics of the infants with HC versus

those without chorioamnionitis. Demographic characteristics such as mean birth weight or gestational age showed no significant difference between groups, nor was there a difference in the antenatal steroid exposure rates (57.8 vs. 59.1%). Table 2 compares the characteristics of infants with and without exposure to antenatal steroids. Clinical characteristics for the two groups were not different.

Neonatal Outcome

Table 3 shows the neonatal outcome parameters of the group with chorioamnionitis and of that without chorioamnionitis. The incidence of early-onset sepsis was significantly lower in the latter group (1.2 vs. 5.6%; $p = 0.038$). These infants also had a lower incidence of severe IVH (0.6 vs. 6.0%; $p = 0.019$). There was no difference in the incidence of RDS, BPD, NEC, IHC, PVL, PDA and mortality between the 2 groups.

The Association of Antenatal Steroid Exposure

The 2 groups are subdivided by antenatal steroid exposure (table 4). In the infants without chorioamnionitis, antenatal steroid exposure significantly reduced the duration of mechanical ventilation (8.0 vs. 2.0; $p < 0.05$). Besides this, the administration of antenatal steroids did not have a significant association with neonatal morbidity in this group. In the infants with chorioamnionitis, the duration of mechanical ventilation was significantly shorter in those with antenatal steroid exposure (3.0 vs. 1.0; $p < 0.05$). Interestingly, in the infants with chorioamnionitis, the incidence of BPD was significantly lower in those with antenatal steroids exposure (40.0% vs. 19.6%; $p < 0.05$), whereas in infants without chorioamnionitis, antenatal steroids did not have a significant effect on the incidence of BPD.

Histological Chorioamnionitis and Neonatal

Outcome: Multiple Regression Analysis

When subdivided by antenatal steroid exposure, in those infants with chorioamnionitis exposed to antenatal steroids, the duration of mechanical ventilation was significantly shorter and, importantly, the incidence of BPD was significantly low (table 4). In infants with chorioamnionitis, the results showed an association with the incidence of BPD and antenatal steroid exposure, so we made a multiple-regression analysis adjusting for gestational age; table 5 shows the relationship of HC to antenatal steroid exposure and neonatal outcomes after adjustment. The use of antenatal steroids showed a significant protective effect on the incidence of BPD in infants with chorioamnionitis (OR, 0.18; 95% CI, 0.05–0.73; $p = 0.007$).

Table 1. Clinical characteristics of infants with and without HC

Clinical parameters	Without HC (n = 168)	With HC (n = 89)
Birth weight, g	1,552.9 ± 503.25	1,505.3 ± 475.22
Gestational age, weeks	30.8 ± 2.34	30.3 ± 2.60
Male	101 (60.1)	52 (58.4)
SGA	12 (7.1)	7 (7.9)
Apgar score (1 min)	6.0 (4.0–7.0)	6.0 (5.0–8.0)
Apgar score (5 min)	8.0 (7.0–9.0)	8.0 (7.0–9.0)
Antenatal steroid use	98 (58.3)	53 (59.5)

Data are presented as mean ± standard deviation for continuous data and n (%) for dichotomous data. Nonparametric data denote the median with interquartile range.

Table 2. Clinical characteristics in infants with and without antenatal steroid exposure

Clinical parameters	No antenatal steroid exposure (n = 106)	Antenatal steroid exposure (n = 151)
Birth weight, g	1,552.9 ± 503.25	1,505.3 ± 475.22
Gestational age, weeks	30.8 ± 2.34	30.3 ± 2.60
Male	101 (60.1)	52 (58.4)
SGA	12 (7.1)	7 (7.9)
Apgar score (1 min)	6.0 (4.0–7.0)	6.0 (5.0–8.0)
Apgar score (5 min)	8.0 (7.0–9.0)	8.0 (7.0–9.0)
HC	36 (34.0)	53 (35.1)

Data are presented as mean ± standard deviation for continuous data and n (%) for dichotomous data. Nonparametric data denote the median with interquartile range.

Discussion

Current literature emphasizes the role of intrauterine infection in the pathogenesis of BPD. However, maternal antibiotic treatment has not been helpful in reducing the incidence of BPD in the prematurely born infant. Another way to approach infection would be to modulate the inflammation associated with it; antenatal steroids given to the mother may be the key in such an approach. Our study analyzed the role of antenatal steroids in mothers with chorioamnionitis and evaluated the association of antenatal steroids and chorioamnionitis. Our results show that premature infants less than 34 weeks' gestation exposed to intrauterine chorioamnionitis were protected

Table 3. Neonatal outcome

	Without HC (n = 168)	With HC (n = 89)	p value
RDS	88 (52.4)	44 (49.4)	0.653
Mechanical ventilation	3.0 (0.0–16.0)	1.0 (0.0–9.0)	0.05
Use of oxygen	8.0 (2.0–38.0)	16.0 (2.0–52.0)	0.37
BPD	44 (27.3)	23 (28.0)	0.906
Sepsis			
Early-onset	2 (1.2)	5 (5.6)	0.038*
Late-onset	26 (15.5)	15 (16.9)	0.774
NEC (≥ grade II)	2 (1.2)	0 (0)	0.549
IHC	17 (10.5)	10 (12.0)	0.713
IVH (≥ grade III)	1 (0.6)	5 (6.0)	0.019*
PVL	9 (5.5)	5 (6.0)	0.678
PDA	67 (39.9)	33 (41.8)	0.445
Mortality	22 (13.2)	9 (10.1)	0.308

Data are presented as n (%). Nonparametric data denote the median with interquartile range.

* p < 0.05.

Table 4. The effect of antenatal steroid exposure

	Without HC (n = 168)		With HC (n = 89)	
	Without AS (n = 70)	With AS (n = 96)	Without AS (n = 36)	With AS (n = 52)
RDS	39 (55.7)	49 (51.0)	17 (47.2)	27 (51.9)
Mechanical ventilation, days	8.0 (1.0–23.0)	2.0 (0.0–8.0) ¹	3.0 (0.0–27.0)	1.0 (0.0–5.0) ²
Use of oxygen, days	12.0 (3.0–38.0)	7.0 (2.0–41.0)	3.0 (0.0–27.0)	12.0 (2.0–39.0)
BPD	20 (30.3)	24 (25.8)	14 (40.0)	9 (19.6) ²
Sepsis				
Early-onset	1 (1.4)	1 (1.0)	1 (2.8)	4 (7.7)
Late-onset	9 (12.9)	17 (17.7)	9 (25.0)	6 (11.5)
NEC (≥ grade II)	0 (0)	2 (1.2)	0 (0)	0 (0)
IHC	10 (14.9)	7 (7.5)	6 (17.1)	4 (8.5)
IVH (≥ grade III)	0 (0)	1 (1.1)	3 (8.3)	2 (4.3)
PVL, n (%)	4 (5.7)	5 (5.4)	3 (8.3)	3 (5.8)
PDA	19 (27.1)	28 (29.2)	9 (25.0)	14 (26.9)
Mortality	10 (14.3)	12 (12.5)	3 (8.3)	6 (11.5)

Data are presented as n (%). Nonparametric data denote the median with interquartile range. AS = Antenatal steroid.

¹ p < 0.05 vs. infants without AS in the group without HC. ² p < 0.05 vs. infants without AS in the group with HC.

from the development of BPD when treated with antenatal steroids. Our study also shows that HC is associated with adverse neonatal outcomes such as early-onset sepsis and severe IVH. After adjustment for gestational age, only severe IVH was independently associated with chorioamnionitis. These findings are consistent with previous studies listed below which suggest the association between the increased incidence of IVH and chorioamnio-

nit. Alexander et al. [17] reported increased IVH and PVL among infants who were born to women with chorioamnionitis. Soraisham et al. [7] also showed that clinical chorioamnionitis is associated with an increased incidence of early-onset sepsis and severe IVH. Our results are in line with these studies that chorioamnionitis is indeed associated with IVH. Been et al. [18] also showed that infants with chorioamnionitis with fetal involve-

ment have higher incidences of NEC, IVH and neonatal mortality. In addition, antenatal steroids significantly improved neonatal outcome, reducing the need for surfactant replacement therapy and the incidence of RDS, IVH and severe IVH [18].

In a meta-analysis of observational studies, Wu et al. [5] showed that clinical chorioamnionitis is associated with cystic PVL and cerebral palsy. Despite early evidence of significant associations between chorioamnionitis and outcome parameters, such as cystic PVL and NEC [19, 20], these were not observed in our study.

There is a lack of evidence on the association of antenatal steroids and chorioamnionitis. Been et al. [21] recently conducted a meta-analysis of observational studies on this matter and our study adds value to previous studies. The use of antenatal steroids improved outcome of infants and we observed no harmful effects; this is in line with Been et al. [21] In addition, Lahra et al. [1] recently showed that chorioamnionitis was associated with a decreased incidence of RDS but not BPD.

There is sufficient evidence linking chorioamnionitis to altered lung maturation and development. The lung outcomes are likely to depend on the type, duration and intensity of the chorioamnionitis as well as other therapies such as corticosteroids. Kramer [22] demonstrated that endotoxin can cause the inflammation/maturation sequence by direct contact with the fetal lung and endotoxin-mediated fetal lung inflammation can cause the anatomical changes of BPD. That study also showed that antenatal corticosteroids initially suppress endotoxin-induced chorioamnionitis in fetal sheep, but amplify the inflammatory responses at later time points. Kallapur et al. [23] also showed the interaction of the corticosteroid and inflammatory pathways in fetal sheep. Antenatal corticosteroids suppress the initial fetal lung inflammation caused by intraamniotic endotoxin, but indicators of inflammation are increased if delivery is delayed for 15 days. Human studies on these interactions are scarce compared to animal experimental studies and it is still to be defined.

Van Marter et al. [24] showed that chorioamnionitis was associated with a decreased risk of BPD if infants were ventilated for less than 7 days. This suggests that antenatal infection or inflammation reduces the risk of chronic lung disease only if the preterm infant was ventilated for several days. This also supports part of the Watterberg effect on BPD, since only ventilated children were included in their initial study; it is interesting to point out that none of the patients reported in the initial Watterberg study received antenatal steroids [6]. Over the

Table 5. HC with antenatal steroid exposure and neonatal outcome – a multivariate model

	aOR (95% CI)	p value
RDS	0.91 (0.33–2.56)	0.864
Mechanical ventilation, days	0.15 (0.04–0.51)	0.003
Use of oxygen, days	0.25 (0.08–0.79)	0.018
BPD	0.18 (0.05–0.63)	0.007*
Sepsis		
Early-onset	2.50 (0.26–23.99)	0.427
Late-onset	0.32 (0.10–1.05)	0.059
IHC	0.35 (0.08–1.43)	0.143
IVH ($\geq$ grade III)	0.47 (0.07–3.00)	0.423
PVL	0.61 (0.11–3.25)	0.558

Estimated OR adjusted for gestational age based on the multiple logistic regression model. aOR = Adjusted odds ratio.

* $p < 0.05$.

last decade, the increased use of antenatal steroids has contributed to an apparent reduction in RDS, but there has been no significant effect on BPD incidence [1]. In addition, many current studies with high rates of antenatal steroid administration do not show as significant an association between chorioamnionitis and BPD as before [25].

In our results, antenatal steroids reduced the use of mechanical ventilation in infants with and without chorioamnionitis which may have reduced further lung injury in both groups. However, only those with chorioamnionitis developed less BPD after antenatal steroid exposure; this suggests at least partly distinct mechanisms are at work between chorioamnionitis and antenatal steroids. More human data and animal studies are needed to explore the underlying mechanisms of pulmonary developmental changes after chorioamnionitis. Other than focusing mainly on the short-term respiratory and neurological outcomes, potential long-term outcomes have still to be defined regarding the concept of chorioamnionitis as a multiorgan disease of the fetus, as suggested by Gantert et al. [26].

The limitations of this study include the relatively small sample size resulting in low power and the exposure to antenatal steroids being relatively low. Imminent preterm deliveries are transferred to our hospital, which does not allow for time for administration of antenatal steroids in a timely manner. Chorioamnionitis classified by the presence of funisitis would provide more value to the study, but a statistical analysis was not conducted due to the small sample size. We are enrolling more cases at

present and are planning further research with a larger sample size and including information on fetal involvement.

In conclusion, HC was associated with severe IVH and early-onset sepsis. In the presence of chorioamnionitis, the incidence of BPD was also low in infants who were exposed to antenatal steroids. Due to the complex interactions of antenatal steroids and chorioamnionitis, there

are numerous factors that contribute to individual outcomes. Therefore, future studies should focus on the immunological mechanisms of these interactions as a potential target to ameliorate the adverse effects. This study evaluates only the short-term outcome on the association between antenatal steroids and chorioamnionitis and more studies are needed to evaluate the long-term outcomes in the aspect of multiorgan disease.

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