Chorioamnionitis, Cortisol, and Acute Lung Disease in Very Low Birth Weight Infants

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ABSTRACT. *Objective.* **To explore the relationship between chorioamnionitis, postnatal cortisol concentrations, and acute respiratory distress in very low birth weight infants.**

Methods. **Appropriate for gestational age infants weighing between 501 to 1500 g at birth were enrolled into this prospective, observational study, and data regarding respiratory distress on the first day of life were recorded. Serum cortisol concentrations were measured on (a) day 2, (b) day 3 or 4, and (c) day 5, 6, or 7 of life. On day (b) or (c), 3.5 μg/kg of cosyntropin (an adrenocorticotrophic hormone analog) was given, and a repeat specimen was drawn 30 minutes later. Chorioamnionitis was diagnosed by placental examination by one author (R.L.N.).**

Results. **Forty-two infants exposed to chorioamnionitis and 37 infants not exposed were enrolled. Chorioamnionitis correlated inversely with gestational age, and was associated with decreased measures of acute respiratory support (exogenous surfactant, fraction of inspired oxygen, and ventilator support at 12 and 24 hours). Infants with chorioamnionitis had higher cortisol concentrations, both basal and stimulated. Gestational age was not significantly related to basal cortisol, but did correlate positively with stimulated values. Cortisol values from the 16 infants exposed to prenatal glucocorticoid therapy were excluded from these analyses.**

Conclusions. **These results provide evidence that prenatal inflammation leads to adrenal stimulation, resulting in increased cortisol secretion and accelerated lung maturation. The enhanced response to cosyntropin stimulation seen in these infants may reflect an increased adrenal capacity to respond to postnatal stressors. Because of the apparent magnitude of the effect of chorioamnionitis on cortisol measures, this factor should be included in future investigations of adrenal function in very low birth weight newborns.** *Pediatrics* **1997;99(2). URL: http://www.pediatrics.org/cgi/content/full/99/2/e6;** ***chorioamnionitis, very low birth weight infants, respiratory distress syndrome, cortisol, adrenocorticotrophic hormone, adrenal gland, lung maturation.***

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ABBREVIATIONS. PROM, prolonged rupture of membranes; RDS, respiratory distress syndrome; IL-1β, interleukin-1β; VLBW, very low birth weight; ACTH, adrenocorticotrophic hormone; RAS, respiratory acuity score; PMN, polymorphonuclear leukocyte; I:T ratio, immature to total neutrophil ratio; PIH, pregnancy-induced hypertension.

The effect of chorioamnionitis on acute respiratory disease in the premature infant is unclear. It has been reported to either increase, decrease, or make no contribution to the incidence or severity of acute respiratory distress in this population.[1–4] These conflicting reports may be due in part to differing definitions (eg, clinical signs of maternal infection versus pathologic examination).

Chorioamnionitis and prolonged rupture of membranes (PROM) frequently coexist.[5] Longer duration of membrane rupture is associated with increasing infiltration of inflammatory cells into the fetal membranes.[6] Additionally, the presence of chorioamnionitis may itself cause rupture of the membranes.[7] Several studies have suggested that PROM confers protection against respiratory distress syndrome (RDS).[8–11] A larger review did not confirm this protective effect.[12]

We postulated that the protective effect attributed to PROM in the earlier studies resulted from the presence of chorioamnionitis. Chorioamnionitis is associated with an increased placental production of interleukin-1β (IL-1β) and other inflammatory mediators.[13,14] IL-1β, in turn, stimulates the release of corticotropin-releasing factor and corticotropin.[15,16] We hypothesized that this process would result in increased secretion of cortisol, with resultant lung maturation. To test this hypothesis, we prospectively studied the relationship of chorioamnionitis to serum cortisol concentrations and to acute respiratory distress in very low birth weight (VLBW) infants.

METHODS

This study was conducted at the Hershey Medical Center of the Pennsylvania State University School of Medicine, and was approved by its institutional review board. Infants admitted to the newborn intensive care unit were eligible for this study if they (1) were 501 to 1500 g at birth, with weight appropriate for gestational age; (2) had no apparent major congenital anomaly; and (3) did not undergo a major surgical procedure during the first week of life. Infants were enrolled after parental consent was obtained.

Surfactant administration was used as a marker for respiratory distress, since it is not administered prophylactically at the Hershey Medical Center. No attempt was made to distinguish whether respiratory distress was caused by pneumonia versus RDS. Congenital sepsis was defined as a positive blood or cerebrospinal fluid culture. Degree of respiratory support was quan-

tified with a respiratory acuity score (RAS) shown to have good correlation with measures incorporating blood gas data[17]: 1 point/cm H_2O inspiratory pressure + 1 point/cm H_2O end expiratory pressure + 1 point/mechanical breath/minute + 1 point/ $\%O_2$ >21%. This score allowed comparison of respiratory support for all infants, whether or not blood gases were obtained. RAS data were recorded daily at 6:00 AM and 6:00 PM The scores closest to 12 and 24 hours of life were used for analysis. White blood cell counts obtained for clinical indications before 6 hours of life were also recorded. All clinical care was at the discretion of the attending physician, who was unaware of the study results.

Day of birth was defined as day of life 0. Blood samples were drawn for cortisol determinations on the afternoon of (a) day 2, (b) day 3 or 4, and (c) day 5, 6, or 7 of life. On either day (b) or (c), the baseline sample was followed by administration of 3.5 μg cosyntropin (α1–24 corticotropin, an adrenocorticotrophic hormone [ACTH] analog). Cosyntropin was permitted to be given intravenously by slow push, or intramuscularly; however, all patients in this study received the medication intravenously. After 30 minutes, another blood sample was drawn for cortisol analysis.

Cortisol concentrations were measured in one laboratory, in duplicate, by radioimmunoassay (Diagnostics Products Corporation, Los Angeles CA). The intraassay and the interassay variabilities for the assay were 5.0% and 7.5%, respectively. Cross-reaction for all other naturally occurring adrenal steroids was less than .1%. All pathologic evaluations of the placentas and fetal membranes were performed by one author (R.L.N.), who was unaware of the clinical care or course of the study patients.

Criteria for diagnosis of chorioamnionitis were those previously described by the author.[6] Briefly, the diagnosis of acute chorioamnionitis was made when polymorphonuclear leukocytes accumulated beneath the chorionic (fetal) plate of the placenta. This finding is classified as stage 1 and studies have shown that it usually persists for the first 3 days after the infecting agents have gained access to the amniotic cavity.[6] During the next 3 to 4 days the leukocytes invade and slowly pass through the chorionic plate (stage 2). When the leukocytes reach the basement membrane just beneath the amnion, the process is at stage 3. It usually takes at least a week for the process to reach stage 3.[6]

Statistical Analysis

Population data were compared by unpaired Student's t test. Linear regression was used to evaluate the relationship of chorioamnionitis to gestational age. After that, the relationship of chorioamnionitis to respiratory distress was analyzed. First, logistic regression was performed to evaluate the effect of gestational age and chorioamnionitis on the administration of surfactant, as a marker for the clinical diagnosis of RDS. Secondly, the effect of gestational age and chorioamnionitis on fraction of inspired oxygen and respiratory acuity score (RAS) at 12 and 24 hours of life was analyzed using multiple regression analysis.

Because study findings might be influenced through enrollment bias, a log was kept of infants otherwise eligible for the study whose parents were not approached because of death before enrollment, or because of clinical instability. Eleven patients were identified as "met criteria, not approached for clinical reasons," and had placental pathology performed. Seven of these infants died. Clinical and pathologic data from this group of patients was added to the analyses to evaluate for enrollment bias. These analyses resulted in no change in statistical significance or trend from that found in the study population.

Serum cortisol concentrations were not normally distributed; therefore, log transformation was performed, which yielded normally distributed data for analysis. Cortisol concentrations are written as nanomoles/liter (= micrograms/dL × 27.6). The effect of exposure to maternal steroids on postnatal cortisol concentrations was evaluated; because day 2 concentrations were significantly lower in these patients, all cortisol values from these patients were excluded from further analysis. No infants received postnatal steroids during the first week of life. The relationship of chorioamnionitis to serum cortisol concentrations was then evaluated with a general linear models analysis of variance, in a model that included gestational age as a cofactor.

RESULTS

Eighty-seven infants were enrolled in the study. Three were excluded from analysis due to: (1) parental withdrawal of consent, (2) diagnosis of congenital adrenal hyperplasia, and (3) a small for gestation patient inadvertently enrolled. Placental pathology was performed on placentas from 79 of the 84 patients (94%). Characteristics of the population are shown in Table 1. The presence of chorioamnionitis correlated inversely with gestational age ($F = 15.56$, $P < .001$). Because of this very strong correlation, gestational age was included as a cofactor in all analyses.

Chorioamnionitis was associated with a decrease in the need for acute respiratory support in this population (Table 2). First, infants with chorioamnionitis were significantly less likely to receive surfactant. In a logistic regression with surfactant administration as the outcome variable, both gestational age and chorioamnionitis contributed significantly to a χ^2 of 22.73 (gestation, 14.05; chorioamnionitis 9.37; both $P < .005$). Adding the factor "exposure to prenatal steroids" (16 infants) produced no significant effect in this analysis (addition to $\chi^2 = .52$, $P = .47$). Secondly, infants exposed to chorioamnionitis required significantly less supplemental oxygen and received less ventilator support at 12 and 24 hours than infants without chorioamnionitis exposure (Table 2).

Nineteen of the infants had rupture of membranes for longer than 24 hours (PROM), and more of these had chorioamnionitis (Table 1). A single factor χ^2 analysis of the relationship of PROM to surfactant administration would have shown a significant relationship ($P = .04$); however, when gestational age was added, and a logistic regression performed, this relationship was no longer significant ($P = .16$). When chorioamnionitis was added to the regression, there was no independent relationship between PROM and surfactant administration ($P = .81$).

Before analyzing the relationship of chorioamnionitis to serum cortisol concentrations, we examined the effect of prenatal exposure to corticosteroids. Sixteen infants had received prenatal steroids (Table 1). Cortisol values were significantly decreased on day 2 in these infants (geometric mean 119 nmol/L vs 213 nmol/L; $P < .001$). Although day 4 and 6 values were not significantly different, we excluded all cortisol data from these infants from analysis.

TABLE 1. Population Characteristics*

	Chorioamnionitis	
	Present (n = 42)	Absent (n = 37)
Birth weight (g)	936 ± 242†	1080 ± 267
Gestation (wk)	26.7 ± 2.1†	28.4 ± 1.8
Race (Caucasian/Black/Hispanic)	36/2/3	33/4/0
Chorioamnionitis stage		
1	10	—
2	10	—
3	22	—
Maternal steroids	10 (23%)	6 (17%)
Rupture of membranes >24°	14 (33%)†	5 (13%)
⊕ Blood/CSF culture	0	0
Died	2 (5%)	3 (8%)

* Data are means ± S.D.
† Significantly different from "chorioamnionitis absent" group, $P \leq .01$.

TABLE 2. Ventilatory Support*

	Chorioamnionitis	
	Present (n = 42)	Absent (n = 37)
Surfactant	27 (64%)†	30 (81%)
FIO_2 12°	.30 ± .02†	.39 ± .03
RAS 12°	60 ± 5†	72 ± 6
FIO_2 24°	.29 ± .01†	.37 ± .02
RAS 24°	48 ± 4†	64 ± 6

* Data are means ± S.E.M.
† Significantly different from "chorioamnionitis absent" group, $P < .005$ (all analyses included gestational age).

Infants exposed to chorioamnionitis had significantly higher serum cortisol concentrations during the first week of life ($F = 8.88$, $P < .005$) (Fig. 1). Gestational age was not a significant predictor of baseline cortisol concentration in this analysis ($F < .01$, $P = .97$), nor was day of life ($F = 2.97$, $P = .054$). Infants exposed to chorioamnionitis also had higher cortisol concentrations after stimulation with cosyntropin (poststimulation, chorioamnionitis group (n = 31) vs nonexposed group (30): geometric mean 463 vs 377 nmol/L, $F = 11.07$, $P < .005$), and a greater increase over their baseline values (stimulated–baseline value, or delta cortisol: geometric mean 252 vs. 210 nmol/L, $F = 10.50$, $P < .005$) (Fig. 2). The day of life that the test was performed was not significant in this analysis. We did not find a significant relationship between stage of chorioamnionitis and either cortisol concentrations or indices of respiratory support; however, the number of patients in each group was small (Table 1). Gestation was significant in these analyses, such that the response to cosyntropin stimulation increased significantly with increasing gestational age (poststimulation, $F = 9.85$, $P < .005$; delta cortisol, $F = 20.84$, $P < .001$).

The presence of chorioamnionitis was also associated with significantly higher peripheral polymorphonuclear (PMN) neutrophil counts, immature PMN counts and immature:total neutrophil (I:T) ratios in these infants immediately after birth (Table 3). Two factors that might affect these numbers are pregnancy-induced hypertension (PIH) and labor. Analyzing patients without PIH, the immature PMN and I:T ratio were still significantly higher in infants with chorioamnionitis, and the total PMN count trended higher. In those patients delivered after labor, total PMNs, immature PMNs, and I:T ratios were significantly higher in patients exposed to chorioamnionitis.

DISCUSSION

In this study, we investigated the relationship of chorioamnionitis to acute respiratory distress in VLBW infants. We found that the presence of chorioamnionitis was associated with a decreased incidence and severity of respiratory disease, measured qualitatively by exogenous surfactant administration, and quantitatively with a respiratory acuity score. In addition, we found that infants exposed to chorioamnionitis had significantly higher serum cortisol concentrations, providing evidence of a possible mechanism for this effect: acceleration of lung maturity through glucocorticoid action.

Previous studies have provided conflicting information about the relationship of chorioamnionitis to acute respiratory disease in the premature infant.[1–4] This disagreement may be due to differing definitions of chorioamnionitis and differing study designs. The strong inverse correlation of chorioamnionitis with gestational age that we and others[17] have found may also have influenced the evaluation of this relationship. In our study, the diagnosis of chorioamnionitis was based solely on placental pathology, and was determined by one experienced investigator. An additional strength of this study is that placental pathology was available for 79 of the 84 patients enrolled.

PROM has also been observed to decrease the incidence of RDS in several studies.[8–11] In addition, one of those studies found that infants with PROM had increased serum cortisol concentrations immediately after birth.[8] A large retrospective review

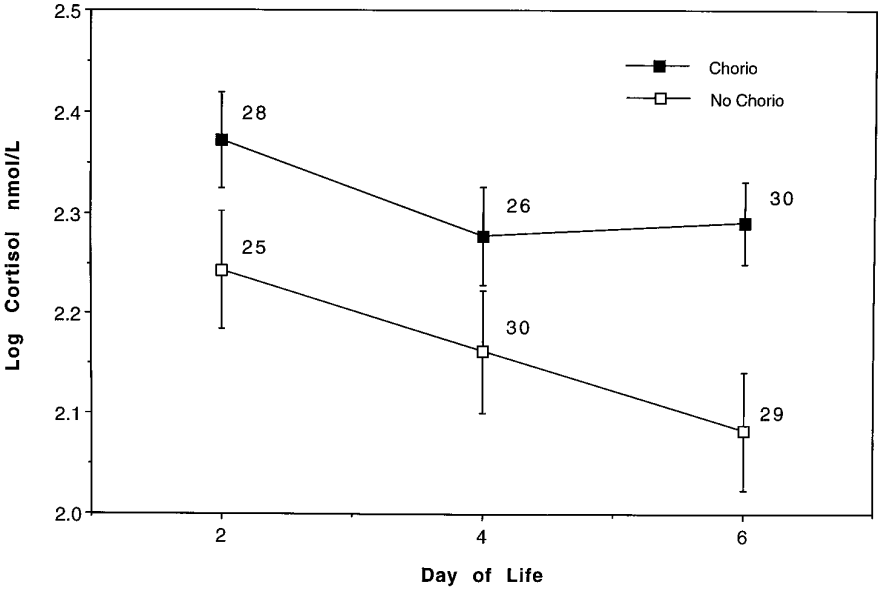

Fig 1. Serum cortisol concentrations, plotted as log cortisol (nmol/L), mean ± SEM, in infants exposed to chorioamnionitis (chorio, ■) versus those not exposed (no chorio, □). Values are different between the two groups ($P < .005$). Geometric mean cortisol concentrations (nmol/L), chorio vs no chorio, were as follows: 235 vs 175, 192 vs 145, 195 vs 121 (nmol/L = (μg/dL) × (27.6)). None of these infants received prenatal or postnatal glucocorticoid.

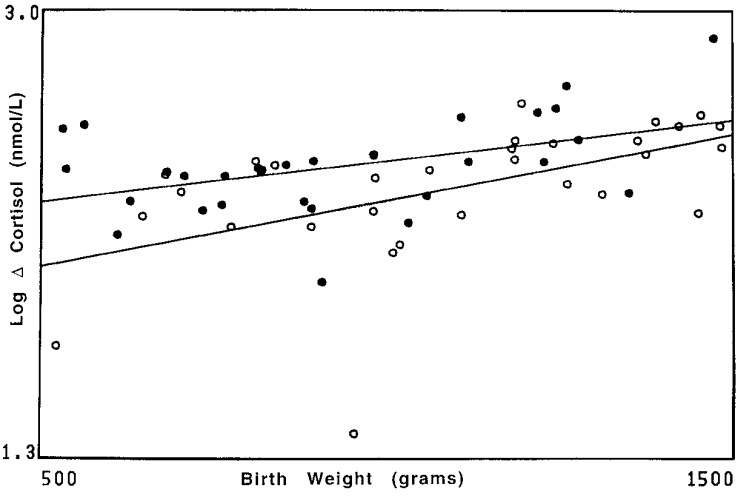

Fig 2. Increase in serum cortisol after cosyntropin (ACTH analog) stimulation, plotted as log (Δ cortisol-(nmol/L)) versus birth weight, where Δ cortisol = [stimulated cortisol]–[baseline cortisol]. Patients exposed to chorioamnionitis (●) had significantly higher values for Δ cortisol than those not exposed (○), (geometric mean 252 vs 210 nmol/L, $P < .005$). Data are plotted using birth weight to better visualize individual data points; however, all analyses were performed using gestational age as a measure of maturation, which was a significant factor in the relationship, $P < .001$. None of these infants received prenatal or postnatal glucocorticoid.

TABLE 3. White Blood Cell Counts*

	Total PMNs	Immature PMNs	Immature: Total PMNs
Chorioamnionitis present (n = 41)	6476 ± 1123	3074 ± 619	0.45 ± .04
Chorioamnionitis absent (n = 35)	2090 ± 304†	423 ± 101†	0.16 ± .03†
Without PIH (n = 11)‡	2845 ± 690	445 ± 147†	0.13 ± .03†
Labor present (n = 7)	1771 ± 363†	257 ± 108†	0.12 ± .04†

* Values are means ± SEM; PMN = polymorphonuclear leukocyte; PIH = pregnancy-induced hypertension.
† $P < .01$ vs chorioamnionitis, analyzed after log transformation.
‡ Excluding patients with the diagnosis of pregnancy-induced hypertension.

failed to confirm a protective effect of PROM against RDS.[12] Because the incidence of chorioamnionitis increases with increasing duration of membrane rupture,[6] PROM may have served as a marker for chorioamnionitis in the previous studies. In our study, we found that an isolated χ^2 analysis would have shown a significant relationship between PROM and a decreased incidence of RDS (as defined by exogenous surfactant administration); however, when gestational age was added to the model, that relationship no longer achieved significance. When chorioamnionitis was added, PROM contributed no significance to the model; however, chorioamnionitis was significantly inversely related to the incidence of RDS.

To investigate the etiology of this inverse relationship, we measured cortisol concentrations in these infants during the first week of life, and found them to be significantly higher in infants exposed to chorioamnionitis. Additionally, these infants responded to cosyntropin stimulation with an increased release of cortisol, compared with infants without chorioamnionitis. These effects were significant through the end of the first week of life. Exogenous corticosteroids have clearly been shown to accelerate lung maturation in the fetus[19] and to decrease the incidence of respiratory distress syndrome in premature infants.[20,21] Together with other studies that have shown lower serum cortisol concentrations in infants with RDS,[22–24] these data provide evidence that an increase in endogenous corticosteroids has a similar effect. We did not find a significant relationship between the duration of chorioamnionitis, assessed by stage, and either cortisol concentrations or measures of respiratory support. This may have been because stage 1 chorioamnionitis persists for several days before progressing[6]; however, the numbers in each group were small.

The increased cortisol concentrations found in infants exposed to chorioamnionitis may result from prenatal stimulation of the hypothalamic-pituitary-adrenal axis by inflammation. Naeye et al[2] demonstrated on autopsy that evidence of antenatal infection was associated with an increase in adrenal weight, as well as with a decrease in hyaline membrane formation in the lung. The increased adrenal weight was due to a greater number of cortical cells in both the fetal and adult (definitive) zones, and to a greater mass of cytoplasm per cell in the adult zone.

Inflammatory mediators such as IL-1β have been shown to stimulate secretion of corticotropin releasing factor and ACTH.[15,16] Placental production of IL-1β is greatly increased in the presence of preterm labor and chorioamnionitis.[13] We have previously found increased IL-1β concentrations in the tracheal lavage fluid of infants exposed to chorioamnionitis.[4] An additional indicator of increased prenatal inflammation in this study is the significant elevation of polymorphonuclear leukocytes in peripheral blood samples.

In these VLBW infants, chorioamnionitis may also underlie the previously observed phenomenon that cortisol concentrations during the first week of life are higher in infants born at very young gestations.[22,25,26] In this study, that phenomenon was explained by the higher incidence of chorioamnionitis at lower gestational age. An analysis examining only the relationship of gestational age to cortisol concentration would have shown a significant correlation

($F = 2.81$, $P = .028$). However, chorioamnionitis, added to the analysis, accounted for more of the variance ($F = 10.4$, $P = .002$), although gestation did not significantly add to the model ($F < .01$, $P = .94$). This study was limited to VLBW infants; therefore, these data do not address the effect of increasing gestation on cortisol concentrations throughout the range of prematurity, an effect that may well be nonlinear in nature.

In contrast, gestation was a significant factor in the ability of these infants to secrete cortisol in response to stress, as we have previously reported.[27] Additionally, we found that infants exposed to chorioamnionitis secreted significantly more cortisol in response to cosyntropin stimulation. The prenatal stimulus of infection, with resultant increase in cell number and cytoplasm in the definitive zone of the adrenal cortex,[2] may increase the adrenal gland's ability to produce more cortisol in response to postnatal stimuli. This more robust response may result in the observed increase in basal and stimulated cortisol values, as well as the finding that these infants require less initial respiratory support.

The prevalence of chorioamnionitis in VLBW infants and the apparent magnitude of its effect on cortisol values in this study would suggest that this factor should be included in future studies of adrenal function in this population. Because infants exposed to chorioamnionitis have less severe acute respiratory illness, studies that aim to evaluate the normal development of adrenal function in premature infants by focusing on relatively well premature infants may be particularly influenced by this factor.

In summary, we have demonstrated an inverse relationship between chorioamnionitis and acute respiratory distress in the VLBW infant, and have suggested a mechanism for this observation: exposure to inflammation leading to increased cortisol production, resulting in accelerated lung maturation. This finding should not, however, dissuade clinicians from administering exogenous corticosteroids to women at risk for preterm delivery, a practice with proven benefit to this population of infants.[20,21] Chorioamnionitis cannot be reliably diagnosed prenatally, and the study population exposed to chorioamnionitis still had a significant incidence of respiratory distress.

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