

Placental and Other Perinatal Risk Factors for Chronic Lung Disease in Very Low Birth Weight Infants

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ABSTRACT

To clarify the relationship between chorioamnionitis and chronic lung disease (CLD) in very low birth weight (VLBW) infants, we performed a retrospective cohort study of all inborn patients between 1995–1997 with gestational age (GA) less than 32 wk, birth weight less than 1.5 kg, survival to 36 wk adjusted GA, and placentas submitted to pathology ($n = 371$). Racial distribution as defined by the mother was 40% white/60% non-white. Prevalence of CLD, defined as O_2 dependence at 36 wk adjusted GA, was 30%. In a preliminary analysis GA and birth weight for GA (standard deviations from the mean, Z-score), considered together, were inversely related to CLD. After adjustment for GA and Z-score, other risk factors for CLD were white race, acute respiratory distress, pulmonary air leak, patent ductus arteriosus, and septicemia. Two placental lesions were inversely related to CLD: histologic chorioamnionitis and acute atherosclerosis (a placental indicator of preeclampsia). Following multivariate

analysis, independent risk factors for CLD were GA (OR, 0.6; 95% CI = 0.5, 0.7), birthweight for GA (OR, 0.4; 95% CI = 0.3, 0.6), white race (OR, 1.9; 95% CI = 1.0, 3.3), patent ductus arteriosus (OR, 2.0; 95% CI = 1.0, 3.5), and pulmonary air leak (OR, 3.0; 95% CI = 1.3, 7.1). Acute atherosclerosis was inversely related to CLD (OR, 0.2; 95% CI = 0.1, 0.8). Chorioamnionitis was stratified by subtype and again no association with CLD was seen in the population as a whole. Finally, chorioamnionitis of all subtypes tended to be increased in white infants and decreased in black infants with CLD. This dichotomy was not explained by differences in death rates, acute respiratory distress, intubation on d 2 of life, or total duration of assisted ventilation. We conclude that while chorioamnionitis was not a risk factor for CLD in our total population, racial differences in its relationship to CLD are worthy of further study. (*Pediatr Res* 52: 713–719, 2002)

Chronic lung disease (CLD) is a major cause of morbidity and mortality among very low birthweight (VLBW, <1.5 kg) infants. Some studies have implicated chorioamnionitis as a risk factor for CLD (1–5). Critical parameters in considering such a relationship include potential confounders such as differences in gestational age and weight for gestational age (fetal growth restriction), the definitions of chorioamnionitis used, and the changing nature of CLD itself. With respect to CLD, recent improvement in the overall survival of extremely low birth weight (<1000 g) infants associated with surfactant, antenatal corticosteroids, and changes in early ventilator management has led to the emergence of a “new” CLD characterized by less airway injury and more pulmonary parenchymal disease (6, 7). In this study we addressed these issues by examining different clinical and histologic subtypes of chorio-

amnionitis together with other potential placental and perinatal risk factors for CLD in a recent cohort of VLBW infants.

MATERIALS AND METHODS

Population. This was a cohort study assessing placental and other perinatal risk factors for CLD in VLBW infants of less than 32 wk GA born between 1995–1997 at the MacDonald Hospital for Women at University Hospitals of Cleveland. CLD was defined as oxygen dependence at 36 wk corrected gestational age. The final study sample of 371 infants was derived from a total population of 490 inborn VLBW infants after the following exclusions: GA greater than 32 wk at birth ($n = 38$), death before 36 wk adjusted GA ($n = 59$), and lack of placental pathology ($n = 22$). The 22 patients lacking placental pathology included 5 with CLD and 17 without CLD. Demographic data (birth weight, GA, and days of oxygen dependence, ventilator dependence, and postnatal steroid therapy) did not differ for infants with and without placental pathology in each group (data not shown). All aspects of the data collection process were in accord with guidelines of the

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Office of Human Subject Research of the National Institutes of Health and had the approval of the University Hospitals Institutional Review Board.

Clinical and Pathologic Data. Obstetrical and neonatal data were extracted from a comprehensive database of all VLBW infants admitted to the neonatal intensive care unit at our institution since 1977 (8). All placentas were examined and processed using a standard protocol with five sections per placenta including two membrane rolls, two sections of umbilical cord, and three parenchymal sections each including the chorionic plate. Placental reports and slides were blindly reviewed and reclassified by a single observer (RWR) using a previously described hierarchical classification scheme (9). Risk factors evaluated in this study included:

Maternal: mean age, age >35 y, history of infertility, previous premature birth, multiple pregnancy, premature rupture of membranes, preeclampsia, clinical chorioamnionitis, prenatal care, genitourinary infections during pregnancy, oligohydramnios, clinical abruptio, chronic vaginal bleeding, tocolytic therapy, antenatal steroids

Placental: histologic chorioamnionitis (maternal response), histologic chorioamnionitis (fetal response), villous edema, findings suggestive of maternal underperfusion, markedly increased syncytial knots, multiple villous infarcts, acute atherosclerosis, thin umbilical cord, chorionic vessel thrombi, perivillous fibrin deposition, chronic deciduitis, decidual plasma cells, membrane hemosiderin, recent retroplacental hemorrhage, monochorionic twinning

Neonatal: birthweight, gestational age, birth weight for GA (Z-score), male sex, white race, Apgar <6, 1 min, Apgar <6, 5 min, acute respiratory distress, Surfactant therapy, patent ductus arteriosus, pulmonary air leak, pulmonary hemorrhage, pneumonia, low thyroxine, septicemia, severe cranial ultrasound abnormalities, necrotizing enterocolitis, hyperbilirubinemia

Our definitions of these risk factors have been previously published (8, 10). Gestational age was the best obstetric estimate (taking into account last menstrual period, ultrasound, and/or early pelvic examination). Birth weight for GA was measured by Z-score (number of standard deviations from the mean for GA) using neonatal data derived from a population similar to our own (11). Race was maternally defined. Acute respiratory distress was defined as oxygen dependence at 2 d of age. Hypothyroxinemia was determined by the state newborn screening test. Patent ductus arteriosus was defined by clinical signs (murmur, bounding pulse, active precordium) with or without further investigation. Pulmonary air leak was the presence of air in the pleural space, mediastinum, or tissue spaces of the lung by x-ray. Septicemia was a positive blood culture. Acute atherosclerosis was medial fibrinoid necrosis and foam cells affecting decidual arteries of the basal plate or membrane role. Clinical chorioamnionitis was defined by maternal fever in the presence of abdominal tenderness, fetal tachycardia, maternal leukocytosis, and/or foul smelling amniotic fluid. Histologic chorioamnionitis was separated into maternal and fetal inflammatory components and subclassified by intensity of the inflammatory infiltrate. Maternal intensity, scored in the worst area of the chorionic plate, was scored as follows: mild-rare neutrophils (<10/high power field), moder-

ate-intermediate neutrophils (11–30/high power field), and severe-abundant neutrophils (>30/high power field). Fetal intensity, based on the intensity of inflammation in the most severely affected chorionic plate vessel, was scored as follows: mild-scattered rare neutrophils, moderate-intermediate neutrophils, and severe-near confluent neutrophils associated with attenuation of the vessel wall.

Statistical Analysis. χ^2 and Fisher exact tests were used for categorical data with significance set at $p = 0.050$. Continuous variables were compared using the two-tailed t test with significance set at $p = 0.050$. Adjusted analyses were performed after correction for GA and birth weight for GA. All individual risk factors significant in the adjusted analyses were entered into a multivariate logistic regression model along with GA and birth weight for GA to identify independent predictors of CLD.

RESULTS

Selected characteristics of the study groups are listed in Table 1. Patients with CLD had significantly lower birth weight, were born at an earlier GA, and were more acutely ill before the development of CLD as estimated by mean days of oxygen, assisted ventilation, and postnatal steroid therapy. Severe fetal growth restriction (Z-score < -2 SD), male sex, multiple pregnancy, preeclampsia, administration of antenatal steroids, and surfactant treatment were comparable in the two groups.

In a preliminary analysis gestational age (GA) was inversely related to CLD (OR, 0.6; 95% CI = 0.5, 0.7). Since low birth weight for GA (Z-score) was more frequent in infants of higher GA (data not shown), we analyzed it together with GA in a logistic regression model. This analysis showed strong independent inverse relationships for both variables with CLD (GA: OR, 0.5; 95% CI = 0.4, 0.6 and Z-score: OR, 0.5; 95% CI = 0.3, 0.6). Although not significant alone, severe fetal growth restriction (Z-score < -2.0 SD) when adjusted for GA was also a strong positive risk factor for CLD (OR, 17.7; 95%

Table 1. Selected characteristics of the study population

	CLD (n = 112)	No CLD (n = 259)
Mean birth weight (g)	813 ± 212*†	1114 ± 238
Mean gestational age (wk)	26.1 ± 2.1*	28.3 ± 2.0
Mean Z-score (SD)‡	-0.01 ± 1.12	0.03 ± 1.03
Mean Oxygen (d)	103 ± 40*	21 ± 21
Mean Ventilation (d)	40 ± 30*	11 ± 12
Mean Postnatal Steroids (d)	34 ± 37*	7 ± 13
Gestational age ≤ 25 wk	43 (38)*§	20 (8)
Z-score < -2.0	7 (6)	10 (4)
Male sex	60 (54)	137 (53)
Multiple pregnancy	26 (23)	63 (24)
Preeclampsia	22 (20)	49 (19)
Antenatal steroids	73 (65)	168 (65)
Surfactant	88 (79)	132 (51)

* $p < 0.050$.

† Mean + SD.

‡ Z-score = SD from mean birthweight for gestational age.

§ Number positive (% positive).

CI = 4.7, 67.0). In light of these data, subsequent analyses were adjusted for both GA and Z-score.

Table 2 lists the other perinatal and placental risk factors that were significantly related to CLD in either the unadjusted or adjusted analyses. Significant in both analyses were acute respiratory distress, pulmonary air leak, patent ductus arteriosus, and septicemia. One minute Apgar score and thyroxine level were no longer significant after adjustment. Histologic chorioamnionitis was unrelated to CLD in the unadjusted analysis and inversely related to CLD after adjustment. Other associations emerging after adjustment were acute atherosclerosis of decidual arteries (inversely related to CLD) and white race (directly related to CLD).

All risk factors significant in the adjusted analysis were entered along with GA and Z-score in a multivariate model (Table 3). GA and birth weight for GA remained significant risk factors for CLD along with white race, pulmonary air leak, and patent ductus arteriosus. Acute atherosclerosis showed a negative association with CLD. Septicemia showed a borderline positive association ($p = 0.054$). Respiratory distress and histologic chorioamnionitis dropped out of the model.

In light of controversy in the literature regarding chorioamnionitis as a risk factor for CLD we performed additional analyses examining specific clinical and pathologic subtypes of chorioamnionitis. Histologic chorioamnionitis was separated into maternal and fetal inflammatory responses and each was further subdivided on the basis of severity as described in the Materials and Methods. No significant relationship of clinical chorioamnionitis or any subtype of histologic chorioamnionitis to CLD was observed in analyses adjusted for GA alone, GA and Z-score, and GA, Z-score, plus all of the significant neonatal risk factors identified in the multivariate model (Table 4).

The relationship of chorioamnionitis to CLD was further explored after stratification by race (Table 5). It should first be noted that chorioamnionitis of all subtypes was much more common in nonwhite infants. In white infants clinical chorioamnionitis showed a borderline significant positive association with CLD ($p = 0.059$) and all subtypes of histologic chorio-

Table 3. Multivariate analysis of risk factors for chronic lung disease

	OR	95% CI
Gestational age	0.6	0.5, 0.7
Birth weight for dates (Z-score)	0.4	0.3, 0.6
White race	1.9	1.0, 3.3
Pulmonary air leak	3.0	1.3, 7.1
Patent ductus arteriosus	2.0	1.1, 3.5
Acute atherosclerosis	0.2	0.1, 0.8
Septicemia	1.7	1.0, 3.1*
Acute respiratory distress	2.5	0.7, 8.9
Histologic chorioamnionitis	0.7	0.4, 1.3

* $p = 0.054$.

amnionitis were more frequent in the CLD group. Conversely, in nonwhite infants CLD was significantly decreased with severe fetal histologic chorioamnionitis (OR, 0.2; 95% CI = 0.4, 0.7) and other measures of clinical and histologic chorioamnionitis were all less common in the CLD group. To further examine this relationship we excluded nine nonwhite infants of other racial backgrounds and looked in more detail at infants identified as either black or white by their mothers.

One explanation for decreased CLD in black infants with chorioamnionitis could be increased early neonatal death in infected gestations. To address this hypothesis, we examined all inborn live births of less than 28 wk gestation admitted to the NICU, stratifying for presence or absence of clinical chorioamnionitis as a predictor of death before 36 wk corrected GA. Deaths were rare in births after 28 wk and only occurred in infants without CA. Only clinical chorioamnionitis could be evaluated in this analysis because histologic data were unavailable in many cases. Interestingly, although not achieving statistical significance, we observed the same racially dichotomous relationship for death at less than 36 wk corrected GA as was observed for CLD. Death was less frequent in black infants with clinical chorioamnionitis (12%, versus 20% without chorioamnionitis) and slightly more frequent in white infants with clinical chorioamnionitis (20%, versus 16% without chorioamnionitis). An inverse relationship between neonatal death and chorioamnionitis in extremely premature infants has been previously described (12).

To better understand the relationships between race, chorioamnionitis, and CLD we evaluated other measures of clinical respiratory status in black and white infants stratified by histologic chorioamnionitis and gestational age (Table 6). No differences in the frequency of acute respiratory distress, duration of ventilation, or duration of oxygen supplementation were noted for either black or white infants born at 28 wk or less. CLD was again less common in black infants and more common in white infants with histologic chorioamnionitis. Restricting the analysis to "sicker" infants who remained intubated on day 2 of life accentuated the differential effects of chorioamnionitis and the inverse relationship between histologic chorioamnionitis and CLD achieved statistical significance for black infants. For infants born after 28 wk there was no relationship between histologic chorioamnionitis and CLD in black or white infants. However, trends were noted suggesting less acute respiratory distress and a shorter duration of

Table 2. Risk factors for chronic lung disease, before and after adjustment for GA and birth weight for GA (Z-score)

	CLD (n = 112)	No CLD (n = 259)	Adjusted OR	95% CI*
Chorioamnionitis				
Histologic (any)	52 (46)†	117 (45)	0.7	0.4, 0.9
Clinical	15 (13)	28 (11)	1.0	0.4, 2.1
Other placental				
Acute atherosclerosis	8 (7)	31 (12)	0.3	0.1, 1.0
Other clinical				
White race	49 (44)	98 (38)	2.0	1.2, 3.5
Apgar <6, 1 min	83 (74)‡	135 (52)	1.5	0.8, 2.6
Acute respiratory distress	109 (97)‡	199 (77)	3.9	1.1, 13.4
Pulmonary air leak	26 (23)‡	10 (4)	3.4	1.5, 7.8
Patent ductus arteriosus	67 (60)‡	65 (25)	2.3	1.4, 4.0
Septicemia	65 (58)‡	80 (31)	1.9	1.1, 3.3
Low thyroxine	31 (28)‡	47 (18)	1.2	0.6, 2.2

* Adjusted for GA and Z-score.

† Number positive (% positive).

‡ $p < 0.050$, unadjusted.

Table 4. Association of subtypes of chorioamnionitis with chronic lung disease

Chorioamnionitis subtype	Prevalence	Adj. GA*		Adj. GA & Z-score†		Adj. GA, Z-score, & Neonatal risk factors‡	
		OR	95% CI	OR	95% CI	OR	95% CI
Clinical	11%	1.0	0.5, 2.0	1.0	0.4, 2.1	1.1	0.5, 2.3
Histologic, maternal							
Any	46%	0.6	0.4, 1.0	0.7	0.4, 1.2	0.8	0.4, 1.4
Severe	5%	0.7	0.3, 2.1	0.6	0.2, 1.9	0.7	0.2, 2.3
Histologic, fetal							
Any	39%	0.7	0.4, 1.1	0.7	0.4, 1.3	0.9	0.5, 1.5
Severe	11%	0.4	0.2, 1.0	0.4	0.2, 1.1	0.6	0.2, 1.5

* Adjusted for gestational age (GA).

† Adjusted for GA and Z-score.

‡ Adjusted for GA, Z-score, and other significant neonatal risk factors (air leak, patent ductus arteriosus, and septicemia).

Table 5. Association of chorioamnionitis with chronic lung disease after stratification by race*

Chorioamnionitis subtype	White infants (n = 147)†			Non-white infants (n = 224)‡		
	Prevalence (%)	OR	95% CI	Prevalence (%)	OR	95% CI
Clinical	4	5.4	1.0, 30.7§	15	0.7	0.3, 1.7
Histologic, maternal						
Any	31	1.1	0.5, 2.5	50	0.6	0.3, 1.2
Severe	3	1.3	0.1, 15.1	6	0.3	0.1, 2.1
Histologic, fetal						
Any	27	1.3	0.5, 3.2	43	0.6	0.3, 1.2
Severe	7	1.5	0.4, 6.3	12	0.2	0.4, 0.7¶

* Adjusted for gestational age (GA) and birth weight for GA (Z-score).

† Prevalence CLD = 33%.

‡ Prevalence CLD = 28%.

§ $p = 0.059$.¶ $p < 0.050$.**Table 6.** Clinical respiratory status in black and white infants stratified by chorioamnionitis and birthweight

Race	Histologic chorioamnionitis (any)	n	Acute respiratory distress	Duration O ₂ (days)	Duration ventilation (days)	CLD (Intubated d 2)*	
						CLD	(Intubated d 2)*
28 Weeks or less gestational age							
Black	+	58	55 (92)	68 ± 41	30 ± 18	23 (40)	23/57 (40)
	−	47	43 (92)	79 ± 41	33 ± 21	27 (57)	27/45 (60)†
White	+	27	26 (96)	73 ± 33	28 ± 17	16 (59)	16/25 (64)
	−	38	37 (97)	72 ± 42	31 ± 19	18 (47)	18/37 (49)
Greater than 28 weeks gestational age							
Black	+	40	25 (63)	12 ± 22	5 ± 9	3 (8)	2/14 (14)
	−	70	48 (69)	19 ± 40	10 ± 28	7 (10)	7/31 (23)
White	+	17	16 (94)	31 ± 38	10 ± 13	3 (18)	3/11 (27)
	−	65	49 (75)	24 ± 28	10 ± 10	12 (19)	11/44 (25)

* Analysis restricted to neonates intubated on day 2 of life (number with CLD/total intubated on day 2).

† $p = 0.049$.

assisted ventilation in black infants with chorioamnionitis and more acute respiratory distress and a longer duration of assisted ventilation in white infants with chorioamnionitis.

Finally, we surveyed risk factors in the white and black populations that might help explain different outcomes with chorioamnionitis (data not shown). In this analysis mothers of black infants were younger, had more antenatal genitourinary tract infections, were more likely to have had a vaginal delivery, and were less likely to have received prenatal care, antenatal tocolytics, or corticosteroids. Mothers of white infants were more likely to have been of advanced maternal age, to

have had a history of infertility, and have carried a multiple gestation. None of the neonatal variables studied differed in the two populations.

DISCUSSION

Chronic lung disease occurs in 10% to 40% of VLBW infants and is a major cause of long term pulmonary complications including recurrent respiratory infections, reactive airway disease, and abnormal pulmonary function (13–15). In addition to respiratory disease, survivors with CLD also have

an increased risk of cerebral palsy, mental retardation, and other less serious motor and cognitive disorders (16, 17). CLD, in most cases, correlates with a pathologic process known as bronchopulmonary dysplasia (BPD). BPD was originally described as an injury pattern primarily affecting large airways caused by the deleterious effects of hyperoxia and barotrauma on the immature lung (18). While these factors continue to play an important role in CLD, recent reports from the era of antenatal steroids and surfactant therapy have emphasized a new pattern of BPD (6, 19, 20). This new BPD is related to developmental abnormalities in alveolar crest formation leading to alveolosaccular and capillary hypoplasia and focal interstitial fibrosis. Investigators have stressed the role of extreme immaturity, nutritional factors, and, in particular, inflammatory mediators in the genesis of this new BPD (21, 22).

CLD may be defined by a variety of criteria including duration of ventilator dependence, oxygen requirements, radiographic appearance, and pulmonary function abnormalities. Although it is generally agreed that a definition relying on pulmonary function is impractical in the intensive care unit setting, some authors have advocated a greater reliance on radiographic features (23). The consensus criterion in most common usage at this time and the one adopted for this study is oxygen dependence at 36 wk corrected gestational age (24).

Strengths of our study include the relatively recent study period (1995–1997) encompassing the new BPD, accrual of cases from a single institution with a longitudinal database, and inclusion of a comprehensive placental analysis using criteria already validated in previous outcome studies of VLBW infants (9, 17). Weaknesses include relatively small sample size and lack of detailed information regarding the early neonatal course (CO₂ levels, fluid requirements, cortisol levels, and indexes of overall illness such as CRIB or SNAP risk scores) (25–29).

Our study confirmed a number of previously described neonatal risk factors for CLD including gestational age, patent ductus arteriosus, pulmonary air leak, and septicemia (26, 30). Other previously reported risk factors significant at the univariate, but not the multivariate, level in our study included decreased thyroxine, early respiratory distress, and low one minute Apgar score (30–32). Previously described risk factors for CLD not significant in our study included male sex, and premature rupture of membranes (33–35). We did find male sex to be significantly increased in infants with CLD in the 1000–1499 g birth weight subgroup (results not shown).

The relationships between fetal growth restriction, maternal hypertension, and lung disease are controversial and complicated by significant overlap between fetal growth restriction and preeclampsia. We found an inverse relationship between birth weight for gestational age (Z-score) and CLD after adjustment for GA. Severe fetal growth restriction as defined by a Z-score more than 2.0 SD below the mean for GA was a highly significant risk factor for CLD, but only after adjustment for GA. Previous studies have reported both positive and negative relationships between fetal growth restriction and neonatal lung disease (36–39). The underlying mechanisms by which growth restriction affects lung function are speculative,

but might be related to some of the well known nutritional and metabolic abnormalities in these patients (40, 41).

Preeclampsia is one of several pregnancy complications in which pulmonary maturity may be accelerated as measured by amniotic fluid phospholipids (45). In one well-controlled study mild-moderate maternal hypertension was associated with a significant decrease in respiratory distress syndrome (42, 43). Clinical preeclampsia was not associated with CLD in our study. However, CLD was decreased in infants with acute atherosclerosis, a placental finding found in a subgroup of preeclamptic mothers (44). Acute atherosclerosis, also known as fibrinoid necrosis of decidual arteries, has been associated with excessive amounts of circulating oxidized lipoproteins and increases in local concentrations of lipoprotein (a) and PDGF- β (45–47). It seems to be a marker for the fulminant acute phase of maternal preeclampsia and is seen in approximately 25% of preeclamptic placentas (unpublished data). One factor that might explain a decreased risk of CLD in infants with acute atherosclerosis is the association of fulminant maternal preeclampsia with fetal neutropenia (48). Neutropenia has a complex relationship with lung injury which can be summarized as follows: neutropenia before birth may limit injury by reducing lung neutrophils while neutropenia developing after birth may aggravate injury because it is commonly associated with increased lung neutrophils resulting from pulmonary sequestration (49, 50).

Recent reviews have stressed the importance of inflammation as a major cause of lung injury in VLBW infants. Evidence cited in support of this hypothesis includes increased levels of antenatal cytokines in amniotic fluid (interleukins (IL)-1, -6, and -8) and cord serum (IL-6) and increased levels of postnatal cytokines (IL-6, TNF), eicosanoids (LTB₄, TXB₂), chemokines (IL-8, MIP-1), platelet activating factor, and neutrophils in the tracheal aspirates of infants who later develop CLD (7, 22, 51–54). The relative roles of antenatal infection (chorioamnionitis), late onset neonatal sepsis, the acute phase response, barotrauma, and the evolving lung disease itself are very difficult to dissect (21, 55, 56). In particular the role of chorioamnionitis in CLD has been controversial. Although most studies have found a positive association, methodologic questions have been raised regarding comparability of birth weights, the definitions of both chorioamnionitis and CLD, the time periods studied, and geographic variation (1–3, 57). After adjustment for gestational age and birth weight for GA, we found histologic chorioamnionitis to be inversely related to CLD. This relationship lost significance when considered along with other risk factors in the multivariate analysis. Further analyses considering clinical and histologic chorioamnionitis subdivided by origin of inflammatory cells (maternal *versus* fetal) and severity of inflammation, failed to reveal any subtype that was positively correlated with CLD.

This study and others have identified white race as an independent risk factor for CLD (30). After stratification by race an interesting dichotomy was observed in the relationship between chorioamnionitis and CLD. Clinical chorioamnionitis was a borderline significant positive risk factor for CLD in white infants and severe fetal histologic chorioamnionitis showed a significant inverse relationship to CLD in nonwhite

infants. Other measures of chorioamnionitis were also increased in white infants and decreased in nonwhite infants with CLD. These differences could not be explained by differences between black and white infants in early neonatal death, acute respiratory distress, duration of ventilation or oxygen supplementation, or intubation status on day 2 of life (early severe illness).

Other investigators have reported racial differences in the susceptibility of VLBW infants to lung disease. White infants are reported to have increased early RDS-related mortality, increased severity of neonatal illness (higher neonatal risk scores), and increased rates of asthma (58–60). Interestingly, a few recent studies have also found that the relationship between chorioamnionitis and neonatal complications such as cerebral palsy in VLBW infants may apply primarily to white infants (61)(J Grether, personal communication). Possible explanations for these differential effects include differing rates of co-morbidities such as severe acute illness, racial differences in cytokine responses or organ susceptibility to cytokines, and different postnatal responses arising secondary to differing *in utero* environments. Our preliminary data showing significant differences in maternal age, infertility, multiple pregnancy, antenatal care, delivery route, and genitourinary infections provide some support for the last explanation. This unanticipated racial disparity in the effect of chorioamnionitis on CLD deserves further study and might explain conflicting data from centers with differing ethnic and racial populations.

CONCLUSION

In conclusion, antenatal factors including gestational age at delivery, fetal growth restriction, and a pathologically defined subgroup of maternal preeclampsia modulated the risk of CLD. Chorioamnionitis did not appear to play a role in the population as a whole, but may have contributed to CLD in white infants. Other risk factors for CLD were all related to the neonatal course and included patent ductus arteriosus, pulmonary air leak, and, possibly, septicemia.

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