Neonatal and Neurodevelopmental Outcomes of Very Low Birth Weight Infants with Histologic Chorioamnionitis

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Objective To determine survival and neurodevelopmental outcomes at 18 months corrected age among very low birth weight infants ≤32 weeks gestation with histologic chorioamnionitis.

Study design Observational, regionalized, single-center cohort study with prospective follow-up.

Results Of the 628 infants meeting the selection criteria, 303 (48%) were born to mothers with evidence of histologic chorioamnonitis. Neonates with histologic chorioamnonitis were of lower gestational age and birth weight. On univariate analysis, they were more likely to have hypotension, bronchopulmonary dysplasia, severe intraventricular hemorrhage, severe retinopathy of prematurity, early-onset sepsis, and death. Infants with histologic chorioamnonitis were more likely to have any neurodevelopmental impairment, specifically, mental delay with a lower mental developmental index. When adjusting for perinatal variables, histologic chorioamnonitis had a protective effect on mortality rates (adjusted OR = 0.44, 95% CI: 0.24-0.8; P = .01; n = 619), had a nonsignificant effect on neurodevelopmental impairment (adjusted odds ratio = 1.33, 95% CI: 0.82-2.17; P = .25; n = 496), and was associated with a 4-point lower mental developmental index at 18-months follow-up (adjusted difference −3.93, 95% CI: −7.52 to −0.33; P = .03; n = 496).

Conclusions Although infants with histologic chorioamnonitis were at an increased risk for death and neurodevelopmental impairment, after multivariate analyses, histologic chorioamnonitis was not associated with adverse long-term outcomes. Results suggest fetal protection from treatment-responsive maternal infection and inflammation. *(J Pediatr 2011;158:397-402)*.

Intrauterine infection is one of many perinatal risk factors that may have an impact on long-term outcomes of very low birth weight (VLBW) infants. Histologic chorioamnionitis is defined by a maternal inflammatory response with neutrophilic infiltration of the membranes or chorionic plate, with or without a fetal inflammatory response, and is the focus of this study.[1]

Chorioamnionitis is often associated with preterm birth occurring in 33% to 57% of placentas of VLBW infants.[2-6] Several studies have reported adverse effects of histologic chorioamnonitis on VLBW outcomes including higher rates of respiratory distress syndrome (RDS), sepsis, intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (cPVL), bronchopulmonary dysplasia (BPD), and death.[7,8] However, there are inconsistencies among the available childhood outcome studies. Rates of cerebral palsy (CP), speech delay, and hearing loss have been reported to be higher in infants born prematurely with histologic chorioamnonitis[9,10] but other studies have found no difference in developmental scores in infancy,[3,6] or CP and neurocognitive outcomes at school age.[11,12] The inconsistencies are attributable to differences in populations and study design, including whether and how potential confounding factors, particularly gestational age (GA), were considered.

The aim of our study was to determine survival and neurodevelopmental outcomes at 18 months corrected age in a cohort of VLBW infants with histologically diagnosed chorioamnionitis. We hypothesized that histologic chorioamnonitis would be associated with death and major neurodevelopmental impairment (NDI) at 18 months.

Methods

We conducted an observational cohort study with prospective follow-up at the Royal Alexandra Hospital, Edmonton, Alberta. This academic hospital is the referral center for high-risk pregnancies and tertiary level neonatal care serving

BPD	Bronchopulmonary dysplasia	MDI	Mental developmental index
BW	Birth weight	NDI	Neurodevelopmental impairment
CP	Cerebral palsy	PROM	Prolonged rupture of membranes
cPVL	Cystic periventricular leukomalacia	RDS	Respiratory distress syndrome
		ROP	Retinopathy of prematurity
GA	Gestational age	VLBW	Very low birth weight
IVH	Intraventricular hemorrhage		

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Northern and Central Alberta. Potential subjects were all inborn infants free of major malformation, admitted between April 1997 and December 2004, with a birth weight (BW) ≤ 1250 g and a GA ≤ 32 weeks. Placentas of these infants were routinely sent for histologic examination. We excluded infants with a BW < 3 percentile,[13] monochorionic twins diagnosed by placental examination, and outborn infants. The infants were followed in the Neonatal Follow-up Clinic. Infants with both placental findings and 18 month neurodevelopmental outcomes available were included. The Human Research Ethics Board of the University of Alberta approved the study protocol and waived parental written consent for the use of an anonymous electronic database and chart review.

Maternal events included clinical evidence of chorioamnionitis, prolonged rupture of membranes (PROM) > 18 hours, antenatal antibiotic use (within 48 hours of delivery), corticosteroid use (any time during pregnancy for premature delivery), and mode of delivery. GA was determined by menstrual history or early antenatal ultrasonography. Clinical or radiologic criteria were used for diagnosing RDS, patent ductus arteriosus, hypotension, and BPD. Serial cranial ultrasonography was done until discharge. IVH and cPVL were defined according to Papile et al,[14] and de Vries et al,[15] respectively. Retinopathy of prematurity (ROP) was defined according to the International Classification of Retinopathy of Prematurity.[16] Sepsis was defined as a positive blood culture result and treatment with antibiotics >48 hours.

Placentas were examined by anatomic pathologists with expertise in placental disease. After delivery, placentas were immediately placed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. Placental examination included cross-sections of the umbilical cord, full-thickness sections of the placenta, and a membrane roll. Cases were classified as chorioamnionitis if there was acute inflammation with polymorphonuclear leukocytes infiltrating the subchorionic fibrin or membrane trophoblast, fibrous chorion, or amnion. A fetal inflammatory response was diagnosed if polymorphonuclear leucocytes were invading the umbilical cord or there was chorionic or umbilical vasculitis. Placental pathology reports were reviewed by a single reviewer (L.R.) and were coded as having evidence of inflammation (chorioamnionitis alone or chorioamnionitis and fetal inflammatory response) or no inflammation (no chorioamnionitis or fetal inflammatory response). Standardized grading (quantitation of the neutrophilic response) and staging of chorioamnionitis was not coded for this study.

Assessment at 18 months included examination by a physiotherapist, occupational therapist, and physiatrist for CP;[17] assessment by ophthalmologist for visual impairment (corrected visual acuity in the better eye < 20/60); and assessment by certified audiologists for hearing impairment (bilateral sensorineural hearing loss > 40 dB at any frequency 250-4000 Hz). Certified psychologists administered the Bayley Scales of Infant Development II that yielded a Mental Developmental Index (MDI) (mean 100; SD 15).[18] An MDI <70 (2 SD below the mean) indicates mental delay. Any NDI was defined as the presence of one or more of the following: CP, visual impairment, sensorineural hearing loss, or mental delay.

Statistical Analyses

Peripartum events and neonatal outcomes were compared according to presence of placental evidence of inflammation (chorioamnionitis with or without fetal inflammatory response *vs.* no chorioamnionitis). Continuous and dichotomous descriptive variables were analyzed with the Student's t test or Mann Whitney U test and the χ^2 test or Fisher exact test, respectively. All P values were based on two-sided test results. Multiple logistic (or linear) regression models adjusting for 7 perinatal factors (PROM, intrapartum antibiotic exposure, antenatal corticosteroids, mode of delivery, GA, sex, and singleton vs multiple) were fitted to determine the effect of histologic chorioamnonitis on death, NDI, and MDI. A backward selection procedure was used to choose the most parsimonious model (reduced model). OR and 95% CI are reported. In addition, 18-month outcomes of infants with chorioamnionitis alone and infants with both chorioamnionitis and fetal inflammatory response were compared. All statistical analyses were performed with SPSS version 14.0 for Windows (SPSS, Inc, Chicago, Illinois).

Results

The study cohort consisted of 721 infants, of which 628 (87%) had both placental disease and 18-month outcomes available (**Figure**). There were 303 infants (48%) with histologic chorioamnonitis.

Mothers with histologic chorioamnonitis were more likely to have clinical chorioamnionitis, PROM, to receive antibiotics, and to delivery vaginally (**Table I**). Neonates born to mothers with histologic chorioamnonitis were of lower GA and BW and were more likely to be singleton. These infants also had higher rates of hypotension, BPD, severe IVH, severe ROP, early-onset sepsis, and death in the NICU in comparison with infants whose mothers did not have histologic chorioamnonitis (**Table I**).

Histologic chorioamnonitis was associated with a higher risk of death in the NICU (unadjusted OR = 1.63) (**Table II**). However, after adjusting for 7 perinatal covariates, histologic chorioamnonitis was found to be protective for death (full model: adjusted OR = 0.44; 95% CI: 0.24-0.8, P = .007, n = 619; reduced model: adjusted OR = 0.51; 95% CI: 0.30-0.87, P = 0.01, n = 619). Other variables in the reduced model protective for death were increasing GA (OR = 0.47; 95% CI: 0.40-0.55, P < .001) and antenatal corticosteroids (OR = 0.32; 95% CI: 0.18-0.58, P < .001). Male sex (OR = 1.59; 95% CI: 0.98-2.60, P = .06) and PROM (OR = 2.36; 95% CI: 1.39-4.02, P = .001) were associated with increased risk of death.

Histologic chorioamnonitis was associated with a higher risk of NDI (adjusted OR = 1.57), specifically mental delay (**Table II**). However, after adjusting for perinatal covariates, histologic chorioamnonitis had no significant