Effect of Chorioamnionitis on Neurodevelopmental Outcome in Preterm Infants
Sharadha Polam, MD; Anne Koons, MD; Mujahid Anwar, MD; Susan Shen-Schwarz, MD; Thomas Hegyi, MD

Objective: To assess the association of neurodevelopmental outcome with the placental diagnosis of chorioamnionitis in very low-birth-weight infants.

Methods: One hundred seventy-seven surviving very low-birth-weight infants, 22 to 29 weeks’ gestational age, born after varying severity of chorioamnionitis, were evaluated at a mean±SD age of 19±6 months’ corrected age with Bayley Scales of Infant Development II and neurologic examination. Select maternal and infant variables were abstracted from the medical records. Neonatal morbidities, Mental Developmental Index (MDI) score, Psychomotor Developmental Index (PDI) score, probability of normal MDI and PDI scores (>84), and cerebral palsy between the chorioamnionitis and the control groups were assessed, controlling for gestational age, sex, and the maternal use of steroids and antibiotics.

Results: The chorioamnionitis group of 102 infants was compared with 75 control infants (mean±SD birth weight, 947±236 g and 966±219 g, respectively; mean±SD gestational age, 26.1±2.8 weeks and 27.1±1.5 weeks, respectively). Infants with chorioamnionitis, compared with controls, had a significantly higher incidence of intraventricular hemorrhage (30% vs 13%) and retinopathy of prematurity (68% vs 42%). Cerebral palsy was diagnosed in 8.6% of the infants with chorioamnionitis and 6.6% of the controls. The MDI and PDI scores were similar between the chorioamnionitis and control groups (mean±SD MDI score, 96±16 vs 97±18 and mean±SD PDI score, 94±19 vs 92±19, respectively).

Conclusions: In very low-birth-weight infants we found a higher incidence of intraventricular hemorrhage and retinopathy of prematurity but similar MDI and PDI scores and risk of cerebral palsy associated with chorioamnionitis.

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Preterm Labor and Delivery continue to occur frequently despite decades of research aimed at their prevention. Prematurity is the leading cause of perinatal morbidity and mortality, and the preterm neonate is estimated to have a 120-fold greater risk of death than the term infant. Infection is implicated as one of the causes of premature labor. Hillier et al have reported positive bacterial cultures from the area between the chorion and amnion after preterm labor in 61% of the women delivering prematurely. Histologic chorioamnionitis occurs more frequently in preterm than in term placentas. In addition to preterm delivery, chorioamnionitis increases neonatal morbidity and mortality. Hagberg et al summarized the sequelae of chorioamnionitis in both term and preterm infants.

A number of studies have examined the relationship of chorioamnionitis and brain injury both in the neonatal period (ultrasoundographic evidence of periventricular-intraventricular hemorrhage and periventricular leukomalacia) and in cerebral palsy (CP). Willoughby and Nelson previously reviewed this data. Postulated mechanisms include cytokine-mediated vascular and microglial injury in the perinatal period.

For premature infants, varying rates of poor performance on the Bayley Scales of Infant Development II (BSIDII) have been reported and may differ considerably between centers. The long-term neurodevelopmental outcome in preterm infants born after maternal chorioamnionitis has not been well studied. The aim of our study was to examine the relationship of histologically diagnosed chorioamnionitis on neurodevelopmental outcome of very low-birth-weight infants born at a gestational age of 22 to 29 weeks.

METHODS

All very low-birth-weight infants free of major malformations, admitted to our neonatal intensive care unit with a gestational age of 22 to 29 weeks, and born between 1997 and 2000 were potential subjects for this observational study. Four hundred thirty-seven infants met these criteria. One hundred eighty-six placentas of these infants had evi...
dence of chorioamnionitis and 251 had no chorioamnionitis. Thirty-seven (20%) of the 186 infants with chorioamnionitis died and 38 (15%) of the 251 infants without chorioamnionitis died. Of the 149 survivors in the chorioamnionitis group, 102 infants who were 12 to 24 months of age, corrected for prematurity, were the subjects of our study (chorioamnionitis group). Of the 213 survivors without chorioamnionitis, a contemporary cohort of 75 infants of similar birth weight followed up in our clinic were the subjects of our control group. Loss to follow-up in both groups was because of postnatal age criteria of 12 to 24 months or relocating out of our area. Select maternal and infant variables were abstracted from the medical records by retrospective review. The institutional review board approved the study.

During the study period, a perinatal pathologist, using a formal placental protocol, examined the placentas of all infants admitted to the neonatal intensive care unit. The pathologist was blinded to the maternal history and graded the placenta as grade 0 (control group) with no evidence of chorioamnionitis in the placenta. Grade 1 or mild chorioamnionitis had a few neutrophils (3-10 neutrophils per high-power field) scattered in the subchorionic space and adjacent chorion; grade 2 (moderate) had many neutrophils (11-30 neutrophils per high-power field) in the lower half of the chorionic plate and the subchorionic space; and grade 3 (severe) had dense infiltrates of neutrophils (>30 per high-power field) throughout the chorionic plate into the amnion.

The developmental outcome was assessed at 12 to 24 months' corrected age, mean ± SD, 19±6 months. Developmental specialists, blinded to group assignment, performed the BSIDII to determine mental and motor developmental indexes (Mental Developmental Index [MDI] and Psychomotor Developmental Index [PDI]). A single pediatrician, who was also blinded to the placental pathologic features, performed a pediatric neurologic examination, using the criteria of Aamiel-Tison. Patients were seen at corrected ages 3, 6, 12, 18, 24, 36, and 48 months as part of the Infant Follow-up Program. For missed appointments, the patient was rescheduled for the next available clinic. The follow-up protocol included an interim history and a complete physical, neurologic, developmental, and language assessment. A neuromotor developmentally trained physician examined all the patients until 12 months of age and those older than 12 months if the PDI score was abnormal. The BSIDII was performed at the 6-, 12-, 18-, and 24-month assessments. The follow-up team consisted of a pediatrician, a nurse coordinator, developmental specialists, and language and physical therapists.

Continuous data are presented as mean ± SD and categorical data are presented as number (percentage). Univariable analysis was done using 1-way analysis of variance and χ² testing when appropriate. Neonatal morbidities, risk of CP, and probability of normal MDI and PDI scores were compared between the chorioamnionitis and control groups using logistic regression analysis, controlling for gestational age, sex, and maternal use of antibiotics and steroids. We defined normal MDI and PDI scores as those higher than 84. The MDI and PDI scores in the 2 groups were compared using multiple regression analysis controlling for these same factors. A P value < .05 was considered significant.

Ten percent of the chorioamnionitis group was classified as mild or moderate, and the degrees of chorioamnionitis did not influence the extent of perinatal morbidity; therefore, we show data regarding presence and absence of chorioamnionitis and not grades of chorioamnionitis. Eliminating the 10% of the cases classified as having mild or moderate chorioamnionitis did not change the results.

Birth characteristics are presented in Table 1. Infants in the chorioamnionitis group had lower gestational ages and their mothers received antibiotics and steroids more frequently than controls. Table 2 presents the medical morbidities in both groups. After controlling for gestational age, sex, and maternal use of antibiotics and steroids, only any grade of periventricular-intraventricular hemorrhage (P = .04) and retinopathy of prematurity (P = .005) were significantly different in the chorioamnionitis group compared with controls. The MDI and PDI scores are presented in Table 3. After controlling for gestational age, sex, and maternal use of antibiotics and steroids, no significant difference was seen in the MDI and PDI scores between the 2 groups or in the percentage of infants in each group with normal MDI and PDI scores. For descriptive purposes, we also looked at the number of infants in each group who scored between 70 and 84 and lower than 70, MDI and PDI scores less than 1 and 2 SDs of the mean, respectively. The numbers were too small for multivariable analysis so the P values refer to univariable analysis. In the chorioamnionitis and control groups, the percentages of MDI scores from 70 to 84 were 2% vs 16% (P = .006) and lower than 70 were 11% and 8% (P = .75). The percentages of PDI scores from 70 to 84 between the chorioamnionitis and control groups were 14% and 15% (P = .89) and lower than 70 were 12% and 16% (P = .31). Cerebral palsy was di-

### Table 1. Characteristics of Study and Control Infants*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infants With Chorioamnionitis (n = 102)</th>
<th>Control Infants (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>947 ± 236</td>
<td>966 ± 219</td>
<td>.57</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>26.1 ± 2.8</td>
<td>27.1 ± 1.5</td>
<td>.005</td>
</tr>
<tr>
<td>Apgar score, 1 min</td>
<td>5.7 ± 2.2</td>
<td>5.8 ± 1.9</td>
<td>.74</td>
</tr>
<tr>
<td>Apgar score, 5 min</td>
<td>7.7 ± 1.4</td>
<td>7.8 ± 1.3</td>
<td>.79</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>54 (45)</td>
<td>39 (49)</td>
<td>.54</td>
</tr>
<tr>
<td>Maternal antibiotics, No. (%)</td>
<td>95 (79)</td>
<td>34 (43)</td>
<td>.001</td>
</tr>
<tr>
<td>Maternal steroids, No. (%)</td>
<td>89 (79)</td>
<td>42 (53)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD unless otherwise indicated. P values are for univariable analysis using analysis of variance or χ² test.

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### Table 2. Select Neonatal Morbidities Analyzed Controlling for Gestational Age, Sex, and Maternal Use of Steroids and Antibiotics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infants With Chorioamnionitis (n = 102)</th>
<th>Control Infants (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLD</td>
<td>49 (40)</td>
<td>21 (25)</td>
<td>.14</td>
</tr>
<tr>
<td>ROP</td>
<td>81 (68)</td>
<td>33 (42)</td>
<td>.005</td>
</tr>
<tr>
<td>IVH (all grades)</td>
<td>36 (30)</td>
<td>10 (13)</td>
<td>.04</td>
</tr>
<tr>
<td>Severe IVH (grades 3 and 4)</td>
<td>11 (9.2)</td>
<td>2 (2.5)</td>
<td>.20</td>
</tr>
<tr>
<td>PVL</td>
<td>7 (5.8)</td>
<td>2 (2.5)</td>
<td>.18</td>
</tr>
</tbody>
</table>

Abbreviations: CLD, chronic lung disease (oxygen dependency at 36 weeks' postconceptual age); IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

*Values are expressed as number (percentage) unless otherwise indicated.
agnosed in 8.6% of the infants in the chorioamnionitis group and 6.6% of the controls (P = .84).

### COMMENT

At a mean age of 19 months, premature infants who had a placental diagnosis of chorioamnionitis showed similar neurodevelopmental outcomes to those who did not have histologic evidence of chorioamnionitis at birth. These findings are based on BSIDII and neurologic examination.

Recent evidence suggests that fetal inflammatory response precedes preterm delivery. Romero et al have shown that a fetal inflammatory response may be followed by the spontaneous onset of preterm parturition. Some of the intraamniotic cytokines that link intrauterine infection with preterm delivery are of fetal origin. Elevated levels of proinflammatory cytokines in the fetal circulation are thought to mediate the increased risk of neonatal morbidities in these infants. Yoon et al have shown that elevated levels of IL-6 in the amniotic fluid and umbilical cord blood were associated with white matter damage and CP in preterm infants. Leitton et al have shown a greatly increased risk of cerebral white matter injury in infants born after fetal vasculitis. Jobe summarized the role of fetal inflammation in the subsequent development of chronic lung disease in extremely low-birth-weight infants.

We did not find an increased risk of neurodevelopmental abnormalities in our cohort of patients with maternal chorioamnionitis, as assessed by MDI and PDI. Similarly, scores lower than 70 were not seen more frequently in our infants who had histologic evidence of chorioamnionitis in comparison with our control infants. Our results are similar to those of Dexter et al who looked at MDI and PDI scores at a corrected age of 7 months and found no difference between infants born after chorioamnionitis and control infants. Most of the outcome data in relation to chorioamnionitis have focused on the development of CP. For full-term infants, there is a strong association of CP with chorioamnionitis but the data are less consistent for preterm infants. As summarized by Willoughby and Nelson, several studies have found an increased incidence of CP after clinical or histologic diagnosis of chorioamnionitis in preterm infants; other studies, however, have been negative. In our study, a similar number of infants in both groups developed CP.

A considerable body of literature implicates very low birth weight as a major risk factor for CP. Rosen and Dickinson reviewed a large number of studies and report a CP rate of 13 to 90 in 1000 live births for newborns weighing 500 to 1500 g at birth. The CP incidence in premature infants varies depending on gestational age and birth weight and is dependent on several other clinical factors. The rates in our study are comparable with those reported. In meta-analysis, Wu and Colford did find a relative risk of histologic chorioamnionitis and CP of 1.6 in the premature population, which is considerably less than the association in term infants (relative risk, 4.7). Several studies reported in the Wu and Colford meta-analysis of preterm infants found no significant association of CP and histologic chorioamnionitis in the preterm. Wu and Colford correctly conclude that further and multicenter collaborations between disciplines are needed to clarify this important issue.

The number of subjects with severe intraventricular hemorrhage and periventricular leukomalacia was small in this study, and we may have missed any increase due to chorioamnionitis. However, as far as normal MDI and PDI scores (>84) are concerned, with a control rate of 76% for MDI and 69% for PDI, to show a 15% difference due to chorioamnionitis, a total of 165 to 200 subjects would be required and to show a 20% difference, a total of 85 to 105 subjects would be required (α error = .05, β error = 0.2). The total number of subjects of 177 in our study is between these estimates. We can thus conclude that it is unlikely that we missed a major difference between the 2 groups in the MDI and PDI scores in the normal range.

Common obstetrical practice at our hospital includes routine use of antibiotics for mothers in premature labor. Likewise, with premature labor, antenatal steroids are used whenever possible. In the control population, there were more deliveries for maternal reasons (eg, pregnancy-induced hypertension [23% in controls vs 5% in the chorioamnionitis group]) or insufficient time from arrival to delivery to obtain a fetal steroid response. These factors likely accounted for differences in steroid and antibiotic use. Although it would be very informative, in this study we did not have enough data to include an accurate diagnosis of clinical chorioamnionitis to compare with the histologic findings and outcome.

Observational studies like ours have to deal with a number of confounding variables. Certain confounding variables in our study are expected to worsen the outcome. These include lower gestational age and more intraventricular hemorrhage in our group of infants with chorioamnionitis. On the other hand, greater use of maternal steroids and antibiotics in our group with chorioamnionitis might have improved their outcome. We therefore controlled for these factors in analysis. Our incidence of severe intraventricular hemorrhage and periventricular leukomalacia was low in both groups. If these brain lesions are important in determining the developmental outcome, their low incidence might explain our results. It is also possible that other determinants of maternal chorioamnionitis, such as clinical signs and symptoms, cord blood cytokine levels, and placental cultures, together with histologic evidence, may better predict infants at risk for long-term adverse outcome. Further, beyond the neonatal pe-

### Table 3. MDI and PDI Scores at 12 to 24 Months of Age Controlling for Gestational Age, Sex, and Maternal Use of Antibiotics and Steroids

<table>
<thead>
<tr>
<th></th>
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<th>Control Infants (n = 75)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI score, mean ± SD</td>
<td>96 ± 16</td>
<td>97 ± 18</td>
<td>.71</td>
</tr>
<tr>
<td>PDI score, mean ± SD</td>
<td>94 ± 19</td>
<td>92 ± 19</td>
<td>.73</td>
</tr>
<tr>
<td>MDI score &gt;84, No. (%)</td>
<td>90 (87)</td>
<td>57 (76)</td>
<td>.17</td>
</tr>
<tr>
<td>PDI score &gt;84, No. (%)</td>
<td>76 (75)</td>
<td>52 (69)</td>
<td>.46</td>
</tr>
</tbody>
</table>

Abbreviations: MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index.
period, many factors influence outcome, including socioeconomic factors, maternal education, birth order, individual recuperative abilities, and subsequent illnesses to name a few. Whether other causes might be contributing to our results was not evident from this analysis.

In conclusion, in extremely premature infants, histologic chorioamnionitis was associated with a higher incidence of retinopathy of prematurity and any intra-ventricular hemorrhage. However, histologic chorioamnionitis was not associated with a reduction in the MDI or PDI scores after 12 months of age or an increased risk of CP, compared with controls.

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REFERENCES