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Are histopathologic chorioamnionitis and funisitis associated with metabolic acidosis in the preterm fetus?

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KEY WORDS
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Objective: Perinatal infection increases the risk of neonatal neurologic injury. Our objective is to determine whether histologically confirmed chorioamnionitis and funisitis is associated with fetal metabolic acidosis.

Study design: This is a retrospective cohort study of all infants 34 weeks or less born at a single tertiary hospital admitted to the neonatal intensive care unit (NICU) between April 1999 and September 2002. Maternal and neonatal records and placental pathology reports were reviewed.

Results: There were 392 infants at 23 to 34 weeks' gestational age admitted to the NICU during this period of whom 354 had placental pathology reported; 259 infants had umbilical cord gases available. These neonates were placed into 3 groups: group 1 (208 infants) had no signs of placental infection, group 2 (59 infants) had isolated chorioamnionitis, and group 3 (87 infants) had both chorioamnionitis and funisitis. The gestational age (30.2 $\pm$ 2.8, 28.3 $\pm$ 3.4, 27.8 $\pm$ 2.8 weeks, $P < .01$) and birth weight (1358 $\pm$ 520, 1242 $\pm$ 547, 1103 $\pm$ 381 g, $P < .01$) were significantly higher in group 1. There was an increase in neurologic morbidity in groups 2 and 3 (25.2%, 34.4%, 43.7%), which was not significant when corrected for gestational age. Groups 2 and 3 had a small but significant increase in umbilical arterial pH (7.25 $\pm$ 0.10, 7.29 $\pm$ 0.10, 7.30 $\pm$ 0.08, $P < .01$) and base excess (-3.5 ± 3.6, -2.2 ± 3.6, -2.3 ± 2.7 mmol/L, $P = .02$). When a single pathologist reviewed all placentas with any inflammation and staged them on the basis of the degree of the fetal inflammatory response, no relationship was found between the degree of fetal inflammation and umbilical arterial pH (stage 1, 7.27 $\pm$ 0.09; stage 2, 7.30 $\pm$ 0.09; stage 3, 7.30 $\pm$ 0.08; $P = .41$) or base excess (stage 1, -2.82 ± 3.47 mmol/L; stage 2, -1.95 ± 3.17 mmol/L; stage 3, -2.23 ± 3.07 mmol/L; $P = .62$). When stepwise multiple linear regression was performed, neither histologic chorioamnionitis nor histologic funisitis were associated with a change in umbilical cord pH or base excess.

Conclusion: Intrauterine infection, as confirmed by histologic chorioamnionitis and funisitis, is not associated with fetal metabolic acidosis. Intrauterine infection may represent a nonhypoxic form of encephalopathy that produces neurologic morbidity by a mechanism independent of hypoxia-ischemia leading to metabolic acidosis.

Increasing evidence supports the view that infants exposed to perinatal infection are at increased risk for

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brain injury. In term infants, there appears to be a 4-fold increased risk for cerebral palsy from chorioamnionitis, and in preterm infants, although not entirely consistent, the estimated increased risk is about 2-fold.[1] The idea that intrauterine infection may be a cause of cerebral palsy is not new. In 1955 Dr Nicholson J. Eastman[2] reported that intrapartum fever was 7 times more common in the mothers of infants with cerebral palsy, and that prolonged neonatal fever (100° F for 3 or more days) was 300 times more common among infants who later had cerebral palsy develop.

The mechanism by which intrauterine infection may be linked with neonatal neurologic morbidity is unclear, but has great implications for determining the time at which injury occurs, and whether this form of injury can be detected by intrapartum monitoring or can be treated by some form of therapy such as maternal antibiotic administration or more rapid delivery. Periventricular leukomalacia is the most severe and frequent cause of cerebral palsy in children surviving preterm birth,[3] and the majority of theories consider the necrotic foci to be hypoxic-ischemic lesions resulting from impaired perfusion at the vascular border zones in "watershed" areas between major cerebral arteries where perfusion pressure is least. These periventricular zones are the most susceptible to a decrease in perfusion pressure and cerebral blood flow. A fetal inflammatory response secondary to infection could lead to fetal hypotension similar to the blood pressure drop seen in septic shock with subsequent decreased perfusion in these vulnerable watershed regions of the fetal brain. An alternate theory is that cytokines produced as part of the inflammatory response to infection are toxic to cells in the fetal central nervous system. It has been shown that tumor necrosis factor and interleukin-6 have a direct toxic effect on oligodendrocytes and myelin leading to white matter damage.[4] Our objective is to determine whether histologically confirmed chorioamnionitis and funisitis are associated with a decrease in umbilical arterial pH or base excess to gain insight into whether neonatal neurologic injury resulting from intrauterine infection occurs through fetal hypotension and resulting metabolic acidosis or through a toxic effect of cytokines on fetal brain tissue.

Materials and methods

This was a retrospective cohort study, approved by our university's institutional review board, consisting of all infants born at a single tertiary care center and admitted to the neonatal intensive are unit (NICU) from April 1999 to September 2002. All maternal and neonatal records were reviewed. Three chromosomally abnormal neonates and 44 neonates with major congenital malformations were excluded. Data abstracted included maternal age, gravidity, parity, race, gestational age at delivery, mode of delivery, birth weight, Apgar scores, umbilical artery pH and base excess, clinical diagnosis of chorioamnionitis, placental pathologic diagnoses, and neonatal morbidity, including respiratory distress syndrome, neurologic morbidity (all grades of intraventricular hemorrhage, periventricular leukomalacia, seizures), necrotizing enterocolits, sepsis, and death. The clinical diagnosis of chorioamnionitis was made in the presence of maternal fever, with the presence of at least 1 other finding of fetal tachycardia, uterine tenderness, or purulent vaginal discharge. Patients diagnosed with clinical chorioamnionitis were immediately started on intravenous ampicillin and gentamicin if not allergic. Cesarean deliveries were performed only for usual obstetric indications. All the placentas in the study were examined by an attending pathologist at our institution. Histologic chorioamnionitis was diagnosed when any polymorphonuclear leukocytes were seen in either the chorion or amnion, or in significant amounts in the subchorionic space. Histologic funisitis was diagnosed when polymorphonuclear leukocytes were seen in the umbilical cord. These patients were divided into 3 groups on the basis of placental histopathology; group 1 consisted of those without evidence of infection (208 patients), group 2 consisted of those with isolated chorioamnionitis (59 patients), and group 3 consisted of those with both chorioamnionitis and funisitis (87 patients). These groups were chosen because clinical chorioamnionitis does not always correlate with histologic chorioamnionitis, and funisitis indicates a fetal inflammatory response, which is more significant than isolated chorioamnionitis. The 59 cases with chorioamnionitis and 87 cases with funisitis were then reviewed by a single pathologist (F.B.A.) who graded the degree of the fetal inflammatory response by using a modification of the criteria of Redline et al.[5] A stage 1 (early) fetal inflammatory response consisted of subchorinoic inflammation in a linear pattern; stage 2 (intermediate) fetal inflammatory response included acute inflammation in the chorionic or amniotic membranes; and stage 3 (advanced) fetal inflammatory response included umbilical cord inflammation with involvement of the veins, arteries, or stroma. In 2 cases, there was concentric umbilical perivasculitis (subacute necrotizing funisitis).

Analysis was performed with 1-way analysis of variance, Scheffé multiple comparison, Fisher exact, and Pearson χ, with $P < .05$ considered significant. Stepwise multivariate linear regression was performed with both cord pH and base excess as the dependent variable. Independent variables included gestational age, intrauterine growth restriction (IUGR), delivery mode, and placental pathologic findings that have been linked with neonatal neurologic morbidity such as histopathologic chorioamnionitis, funisitis, chorioangiosis,