OBSTETRICS

Correlation between initial neonatal and early childhood outcomes following preterm birth

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OBJECTIVE: Neonatal diagnoses are often used as surrogate endpoints for longer-term outcomes. We sought to characterize the correlation between neonatal diagnoses and early childhood neurodevelopment.

STUDY DESIGN: We conducted secondary analysis of a multicenter randomized controlled trial of antenatal magnesium sulfate vs placebo administered to women at imminent risk for delivery <32.0 weeks to prevent death and cerebral palsy in their offspring. Singletons and twins delivering 23.0-33.9 weeks who survived to hospital discharge and had 2-year-old outcome data were included. Those surviving to age 2 years were assessed by trained physicians and the Bayley II Scales of Infant Development Mental Development and Psychomotor Development Indices. Neonatal diagnoses at the time of each baby's initial hospital discharge were examined singly and in combination to determine those most predictive of childhood neurodevelopmental impairment, defined as a childhood diagnosis of moderate/severe cerebral palsy and/or Bayley scores >2 SD below the mean. Data were analyzed by multiple regression models and area under receiver operating characteristic curves.

RESULTS: A total of 1771 children met criteria. Children were delivered at a mean of 29.4 weeks' gestation. In all, 459 (25.9%) had neurodevelopmental impairment. In models controlling for gestational age at delivery, maternal education, maternal race, tobacco/alcohol/drug use during pregnancy, randomization to magnesium, fetal sex, and chorioamnionitis, individual neonatal morbidities were moderately predictive of childhood neurodevelopmental impairment (best model area under receiver operating characteristic curve, 0.68; 95% confidence interval, 0.65—0.71). Combinations of 2, 3, and 4 morbidities did not improve the prediction of neurodevelopmental impairment.

CONCLUSION: Approximately 1 in 4 previously preterm children had neurodevelopmental impairment at age 2 years. Prediction of childhood outcomes from neonatal diagnoses remains imperfect.

Key words: neonatal outcomes, neurodevelopment, prematurity

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Preterm delivery <37 weeks' gestation remains the leading cause of neonatal and childhood morbidity among nonanomalous infants in the United States and the developed world.[1,2] Recent advances in perinatal and neonatal medicine over the last 2 decades have resulted in substantial increases in survival among premature infants.[3] However, this survival increase may be accompanied by an increase in survival with subsequent major morbidities, resulting in sicker children who require intensive postnatal medical care and costly developmental services.[4] Among the most premature, those children born <1000 g, approximately 10-15% develop moderate to severe cerebral palsy and 30% have deficits in cognitive development.[5-7]

Frequently, obstetric and pediatric researchers use neonatal morbidity as a surrogate outcome for longer-term, childhood outcomes when studying pregnancy exposures and/or interventions. While risks factors such as extremely low birthweight (<750 g), early gestational age (<28 weeks' gestation), chorioamnionitis, intracranial hemorrhage, and fetal sex have been identified, the correlation between neonatal and childhood outcomes is imprecisely defined.[8,9] Additionally, many preterm infants acquire multiple neonatal morbidities, but it remains uncertain if this confers an additive risk for adverse childhood neurodevelopment.

Previous studies have been limited. Schmidt et al[9] recently examined 3 neonatal diagnoses: bronchopulmonary dysplasia (BPD), brain injury (defined

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as intraventricular hemorrhage, ventriculomegaly, and/or periventricular leukomalacia), and severe retinopathy of prematurity (ROP), diagnosed singly or in combination, with adverse neurodevelopmental outcomes at 18 months among infants delivered very prematurely (birthweight 500-999 g). These researchers found a correlation between the number of neonatal diagnoses and 18-month outcomes. Babies with all 3 of the studied diagnoses had an 88% chance of adverse childhood outcomes compared to an 18% chance if the infant had none of these diagnoses. The impact of other factors, including other major neonatal morbidity such as necrotizing enterocolitis, and pregnancy or antenatal characteristics such as chorioamnionitis, could not be assessed. Furthermore, it is unknown if these results are applicable to a wider range of the preterm population or are limited to the extremely low birthweight neonate.

The purpose of this study was to determine the relationship between neonatal diagnoses prior to initial hospital discharge and neurodevelopmental outcomes at age 2 years among a large, prospectively collected cohort of infants delivered preterm between 23-34 weeks' gestation.

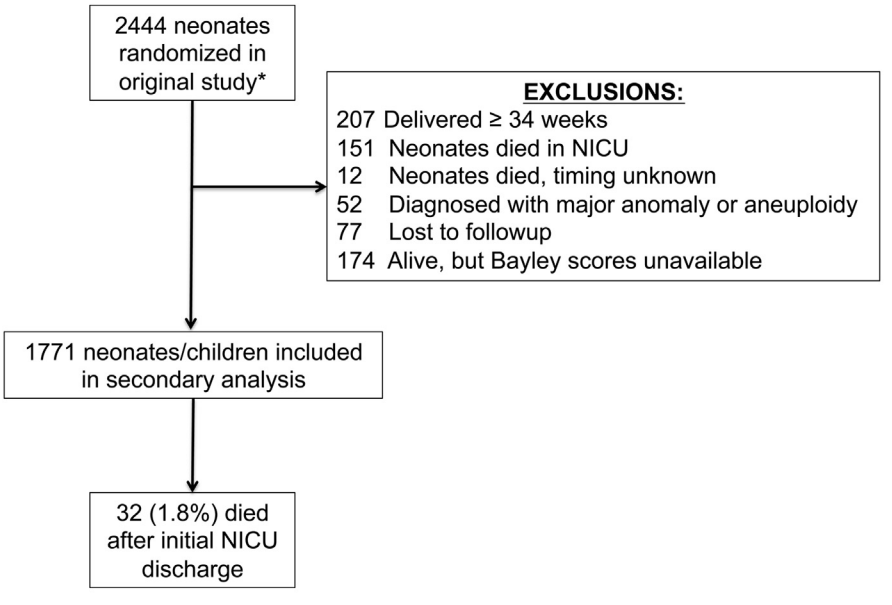
Materials and Methods

This is a secondary analysis of a multicenter randomized controlled trial conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network of antenatal magnesium sulfate vs placebo administered to women at imminent risk for preterm delivery <32.0 weeks' gestation. The aim of this study was to investigate the role of magnesium in the prevention of death and cerebral palsy in their offspring. The methods and results from the primary study have been previously published. Briefly, the main trial found that fetal exposure to magnesium sulfate did not reduce the combined risk of moderate or severe cerebral palsy or death, but the rate of cerebral palsy was reduced among survivors.[10] All participants provided written informed consent at the time of enrollment in the original study. This secondary analysis was performed on a deidentified dataset, and was reviewed by our local institutional review board and determined to be nonhuman subjects research and therefore exempt from institutional review board approval.

Singleton and twin infants admitted and randomized between 23.0-31.9 weeks' gestation and delivered <34.0 weeks' gestation who survived to hospital discharge postbirth and had childhood outcome data at age 2 years were included in this secondary analysis. Infants delivered with chromosomal abnormalities or major congenital malformations and/or with incomplete outcome data at hospital discharge or 2 years of age were excluded. Gestational age was determined by the best obstetric estimate per previously published criteria.[11] Trained research nurses obtained data on neonatal outcomes during hospitalization and at discharge, and at scheduled follow-up visits at 6, 12, and 24 months of age (corrected for prematurity). Specifically, each neonate was assessed for the presence or history of intraventricular hemorrhage, periventricular leukomalacia, BPD, ROP, and necrotizing enterocolitis. Additionally, charts were reviewed to determine if the neonate had ≥1 documented (culture-proven) episode(s) of sepsis during their hospitalization.[10]

Trained pediatricians or pediatric neurologists also evaluated those children who survived to age 2 years. Each child was assessed for the presence of cerebral palsy. When cerebral palsy was diagnosed, the Gross Motor Function Classification System was used to assess severity. Additionally, each child was evaluated with the Bayley II Scales of Infant Development Mental Development Index (MDI) and Psychomotor Development Index (PDI). We defined childhood neurodevelopmental impairment as a diagnosis of moderate or severe cerebral palsy and/or Bayley MDI and/or PDI scores >2 SD below the mean. Babies who survived to initial hospital discharge but died prior to 2-year follow-up were considered to have met the primary adverse childhood outcome.

FIGURE
Eligibility and inclusion in current study



*2241 women were randomized; there were 203 twin pregnancies

NICU, neonatal intensive care unit.

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