School Outcome in Late Preterm Infants: A Cause for Concern

The literature in neonatology is unique in its substantially greater emphasis on long-term outcome studies of newborn infants and young infants who have been exposed to novel therapies. These studies have provided invaluable data regarding the extended safety and efficacy of such therapies and have guided us in the management of vulnerable populations entrusted to our care. In the absence of long-term follow-up data, such as those related to the neurologic injury caused by prolonged postnatal dexamethasone treatment,[1] adverse effects that take a long time to become apparent would have been harder to uncover. Needless to say, the growing brain and body are deceptively capable of keeping adverse effects masked until cognitive and motor functions can be meaningfully tested. It is only then that patterns of functional impairment that no longer fall under the bell-shaped curve become evident.

Certain groups of infants, though, have been ignored in follow-up, largely because they were thought to be at low risk for permanent impairments. Late preterm infants (34 0/7 to 36 6/7 weeks' gestation, also referred to as "near term") offer one such example.[2] Their reputation for being prone to transient clinical problems may have led to a less rigorous approach to their perinatal and postnatal management and to the absence of prospective data sets that track outcomes. Recent observations of significantly higher neonatal morbidity and mortality have raised concerns about these issues, and studies that the late preterm brain can be at risk for periventricular leukomalacia have further fueled this anxiety.[3-6] Problems reported in late preterm infants include delayed lung fluid clearance (transient tachypnea of the newborn infant), respiratory distress syndrome, pulmonary hypertension, apnea, temperature instability, hypoglycemia, jaundice, and poor feeding.[7-11] Little, however, is known about the long-term impact of these neonatal morbidities.

In this month's issue of *The Journal*, a report by Chyi et al[12] examines school outcomes from kindergarten to grade 5 of infants born at 32 weeks to 36 weeks' gestation. When compared with a large group (n = 13,671) of term infants followed in the Early Childhood Longitudinal Study-Kindergarten Cohort (ECLS-K), late preterm infants (n = 767) had lower reading and math scores than their term counterparts in 1st grade. Late preterm infants also had higher participation in special education during early grades and higher odds for below-average reading skills in all grades, although there was resolution of test score differences by the 3rd and 5th grade. What is most striking about these observations is that the late preterm infants included in the study were presumably healthy, had no reported "neonatal compromise," and would have been completely missed even if neurologic follow-up and early intervention programs were in place for high-risk infants. The ECLS-K study followed a nationally representative sample of infants in their kindergarten year (1998 to 1999, class of 2012) to the 8th grade. Prematurity was assessed through parental report, and this, as the authors note, is a weakness of the study. There are other limitations to the study. No information is available in the study about the potential illnesses and/or hospitalizations in the neonatal period because the study involved secondary analysis of the ECLS-K data set and the de-identified participants could not be linked to their medical records. Given the high rates of reported problems after discharge such as hyperbilirubinemia, dehydration, sepsis, and poor feeding, such information would have been critical in differentiating complications that could have contributed to the observed neurologic injury.[13-15] As with many longitudinal follow-up studies in the United States, substantial attrition of numbers at 3rd and 5th grade also affect the quality of conclusions drawn.

These drawbacks notwithstanding, the conclusions of this study could have substantial public health impact because late preterm infants account for 3 of every 4 preterm births in the United States and are on the rise.[16] Higher vulnerability to developmental impairment in up to 10% of all births in the country should be of concern to all. A recent study by Lindstrom et al[17] evaluated a Swedish national cohort of 522,310 infants born in 1973 to 1979 for disabilities and income recorded in national registers in 2002 (age of subjects, 23 to 29 years). Infants of 33 to 38 weeks' gestation accounted for 74% of the total disability associated with preterm birth.

There is, however, another vexing issue: We are not sure of what caused the poorer cognitive outcome in late preterm infants. What came first, the neurologic injury or late preterm birth? It is indeed possible that prenatal events that trigger spontaneous preterm birth (preterm labor and preterm rupture of membranes) are but manifestations of a larger underlying cascade of events that cause or predispose the infant to neurologic injury. Or, is it possible that for infants who are delivered electively for less clear-cut indications and develop neonatal complications, the bulk of the injury occurred in the postnatal period and was potentially preventable?

In either case, the vulnerability of the late preterm brain should be readily evident from the fact that the last 6 to 8 weeks of pregnancy are respon-

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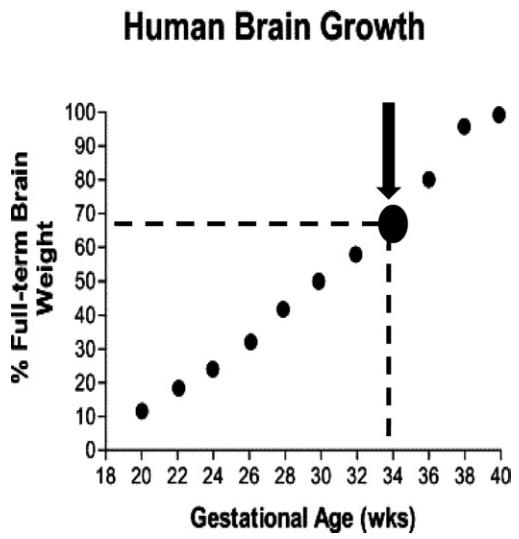

Figure. Brain weight at different ages from 20 to 40 (term) gestational weeks is expressed at each age as a percent of term brain weight. At 34 gestational weeks, the overall brain weight is 65% of term weight. The percent brain weights are based on the data of Guihard-Costa and Larroche,[20] reproduced with permission from H. C. Kinney.[6] Arrow highlights brain weight at 34 weeks' gestation.

sible for a nearly 35% increase in brain size (Figure), a 5-fold increase in white matter volume, structural maturation with increased neuronal connectivity, dendritic arborization, synaptic junction formation, and parallel maturation of neurochemical and enzymatic processes.[6] Thus, although the overall risk of intraventricular hemorrhage and brain injury is far less than that observed in the very low birth weight infants, the predisposition to injury under adverse circumstances could be substantially higher than that seen at term gestation.

There is an urgent need to validate these observations with prospectively collected data on short- and long-term outcomes of late-preterm infants, along with meticulous documentation of events leading to late preterm birth. The questions that need to be addressed are straightforward: Are late preterm infants at risk for permanent neurologic injury, and, if so, why? Answers to these questions could have broad implications for how the obstetrical community approaches threatened or medically indicated delivery at 34 weeks and beyond. In the meanwhile, publications highlighting morbidity and mortality in late preterm infants are forcing us all to pay more attention to this vulnerable population and have led to efforts to standardize care.[18] There is also a renewed commitment on the part of the scientific community to fill the gaps in our knowledge in this area. One such area that needs testing is the role of antenatal steroids in anticipated deliveries at late preterm gestations.[19] For interventions that could ultimately affect up to 10% of our children, the stakes are clearly high.

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