Modern Management of Preterm Infants Prevents Adverse Developmental Outcomes From Hypoglycemia

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In 2009, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development reported on a 2008 conference, "Neonatal Hypoglycemia,"[1] noting that "There has been no substantial evidence-based progress in defining what constitutes clinically significant but transient neonatal hypoglycemia," "There is no evidence-based study to identify any specific plasma glucose concentration (or range of glucose values) to define pathologic 'hypoglycemia,'" and "Research studies are needed to fulfill this basic gap in knowledge and to help demonstrate the relationship between plasma glucose concentrations during the neonatal period and later neurological outcomes." Since that report, there still are no prospective controlled trials to assess risks of any "low" glucose concentrations, their duration, their relationship to other concurrent pathology, or whether treated or untreated, the outcomes differ in any population of newborn infants.

The significance of early postnatal low glucose concentrations, therefore, and their optimal management remain poorly defined. Especially problematic is our inability to sort out healthy neonates with transient low glucose concentrations from those in whom the low glucose concentrations are causing harm or are early harbingers of rare, but more pathologic conditions (congenital hyperinsulinism, metabolic disorders, hypopituitarism).[2] Given the lack of evidence demonstrating an ideal management strategy, it is not surprising that guidelines for screening, diagnosing, preventing, or treating low glucose concentrations in term and late preterm neonates remain varied.[2–4]

The evidence base is not much better for preterm neonates. One important difference between preterm and healthy term neonates, however, is that all preterm infants, especially those <32 weeks gestational age at birth, are at increased risk for worse neurodevelopmental outcomes.[5] Because of this, changes in practice over the past several decades have led to more aggressive prevention of the previously documented high risk of hypoglycemia.[6] As a result, it is nearly impossible today to find a preterm infant who does not receive intravenous dextrose soon after birth. Furthermore, intravenous infusion rates are usually between 4 and 8 mg/min/kg, which, when coupled with persistent endogenous hepatic glucose production,[7] provide more than sufficient glucose to meet normal metabolic requirements and achieve adequate plasma glucose concentrations.

This evolution of practice may be one explanation for the conflicting results from 2 seminal articles on hypoglycemia in preterm infants and long-term outcomes.[8,9] Lucas et al[8] reported retrospective results showing that repeated glucose concentrations

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≤47 mg/dL in asymptomatic preterm infants were associated with worse developmental outcomes, at least to 18 months of age. In contrast, Tin et al[9] reported a similarly designed study that found that asymptomatic preterm infants with repeated blood glucose concentrations ≤45 mg/dL did not have worse outcomes compared with matched normoglycemic infants. Although other differences exist between the 2 studies, a more aggressive approach to parenteral and enteral nutrition may have played a role in the discrepancy between the studies.

If evolution of NICU care of the preterm infant has decreased the incidence, severity, and duration of neonatal hypoglycemia, it is not surprising that in this issue of *Pediatrics*, Goode and colleagues[10] provide new evidence from a multicenter study with 743 infants of ∼32 weeks' gestation that shows no significant differences in intellectual/cognitive skills or academic achievement from 3 to 18 years of age between preterm infants with and without documented hypoglycemia (defined by 3 low glucose ranges or as ≤45 mg/dL). Although low glucose concentrations were not prevented in this cohort, it is not likely that these infants or those without hypoglycemia did not receive current, standard intravenous dextrose infusions and early enteral feedings. Such parenteral and enteral treatment details are not presented in the report. Regardless, this study is important for supporting current standard of practice efforts to provide early intravenous dextrose and nutrition in these preterm infants by showing no adverse long-term neurodevelopmental outcomes specific to low glucose concentrations. The results of this study are consistent with a recent report in late preterm and term neonates (large for gestational age, small for gestational age/intrauterine growth restricted, or infant of a diabetic mother) with asymptomatic hypoglycemia, who, with early enteral feeds, buccal dextrose gel, and/or intravenous dextrose were treated to maintain glucose concentrations ≥47 mg/dL. These infants had similar outcomes as those without any documented low glucose concentrations.[11]

Furthermore, many of the risks of overtreating hypoglycemia in the more preterm patients in the study by Goode and colleagues,[10] such as separation from the mother, admission to the NICU, reduction of breastfeeding, or placement of intravenous catheters, are more likely to be present in very preterm infants. Clinicians should be reassured, therefore, that the current broad range of clinical practices using early intravenous dextrose and enteral feeding will not result in later life adverse neurodevelopmental, cognitive, and academic outcomes due to mild and transient hypoglycemia.

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