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Neonatal Hypoglycemia—Answers, but More Questions

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In this issue of The Journal, Harris et al report the incidence of blood glucose concentrations ≤2.6 mM (47 mg/dL) and ≤2.0 mM (36 mg/dL) in the first 48 hours after birth for 4 at risk populations of neonates. The patient populations included infants of diabetic mothers (IDM), late preterm infants (35–37 weeks gestation), small infants (≤10th percentile or ≤2500 g), and large infants (≥90th percentile or ≥4500 g). They found 51% of these patients had at least 1 blood glucose concentration ≤2.6 mM and 19% had a blood glucose concentration ≤2.0 mM.[1] Advantages of the Harris et al study, compared with some previous studies, include the fact that these infants' blood glucose concentrations were being measured as part of a prospective interventional trial designed to test the effectiveness of a dextrose gel for managing low glucose concentrations. The results of this intervention are not currently reported. This likely resulted in a more standardized schedule and method of collection, processing, and measurement. They also used a glucose oxidase method for the initial measurement as opposed to a less precise “bedside” screening method. These results are quite timely, as a practical guide for screening these same groups of neonates was recently published by the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn.[2] A 51% prevalence of low glucose concentrations supports the decision of the AAP to focus recommendations on these patients. However, despite the important data provided by Harris et al, the clinical problem of neonatal hypoglycemia and the field of glucose metabolism continue to be plagued by insufficient data and unanswered questions.[3]

Around the time of birth, there is a transient rise in fetal glucose concentrations from glycogenolysis and gluconeogenesis. This is followed by a rapid decline in neonatal glucose concentrations after birth and loss of the placenta to a nadir at 1–2 hours of age and then a rise to levels that are similar to late gestation fetal glucose concentrations (about two-thirds of normal maternal values) by 2–4 hours of age. Neonatal glucose concentrations then remain less than adult levels, tending to rise slowly until consistent with adult levels at 3–4 days of age.[4–6]

“Why” does this happen? The advantages of lower neonatal glucose concentrations compared with adult levels for 3–4 days are not clear. The fall in glucose concentrations right after birth appears essential to stimulate physiological processes that are necessary for postnatal survival, such as promoting glucose production by gluconeogenesis, stimulation of appetite, adaptation to fast/feed cycles, and enhancement of oxidative fat metabolism. Also, persistently lower neonatal glucose concentrations might be the result of mechanisms that were vital for the fetus to allow maternal-to-fetal glucose transport and cannot be quickly reversed after birth. Regardless of “why” neonatal glucose concentrations are initially less than adults, this is a consistent condition found in all mammals. But how one views the

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answer to “why” this happens will inform their opinion on the debate over whether these concentrations, especially at the lower end of normal ranges, are harmful. Most agree that symptomatic hypoglycemia should be treated, as should extremely and/or persistently low glucose concentrations, although there is no agreement on which glucose concentrations and after what duration and in relation to other physiological conditions (eg, brain blood flow) irreversible neuronal injury occurs, or on the optimal treatment strategies of any low glucose concentration, let alone whether such treatment strategies improve outcomes.[7,8]

The importance of early identification, prevention, and treatment of low glucose concentrations in certain conditions, such as genetic defects in specific metabolic pathways (eg, fatty acid oxidation disorders) or defects in the regulation of insulin secretion leading to hyperinsulinemic hypoglycemia, is generally agreed upon.[8] However, in the populations studied by Harris et al, the data are less clear. Furthermore, there is little consensus regarding the significance of transient and asymptomatic low glucose concentrations. Most data indicate that adverse outcomes do not occur with such conditions[9]; therefore, it can be argued that treatment other than normal care is not indicated. However, transient, asymptomatic low glucose concentrations may herald metabolic disorders that can cause serious injury. Therefore, some would suggest that caregivers be vigilant to look for further low glucose concentrations, signs of serious hypoglycemia, and make sure that such infants do not go home from the newborn nursery without solid evidence that they can maintain normal glucose concentrations through normal fast-feed cycles.

As with normal infants with transient, asymptomatic low glucose concentrations, there is no evidence demonstrating improved outcome following identification and treatment of low glucose concentrations in IDMs, late preterm infants, small infants, and large infants studied by Harris et al. The AAP recognized that screening and management of asymptomatic low glucose concentrations in these populations is a “controversial issue for which evidence is lacking but guidance is needed.” This led to the recent publication of the updated guidelines.[2] The authors of the guidelines recognized the normal 1- to 2-hour nadir in glucose concentrations and proposed different thresholds for action based on age. Furthermore, older literature shows that IDM and large infants have their first documented low glucose in the first 12 hours after birth whereas late preterm and small infants can have theirs for as long as the first 24 hours.[10–12] Therefore, the guidelines state that screening could be stopped at different times depending on the risk factor. Screening may be stopped for IDM and large infants at 12 hours and for late preterm and small infants at 24 hours, if asymptomatic and with normal glucose concentrations in each case. Predictably, opinions regarding the new guidelines are mixed. Opinions about any guideline, which is precise enough to be practical, will evoke mixed opinions and debate.

How can the data presented by Harris et al inform this debate? First, they found no differences in the incidences of low glucose concentrations in the 4 patient populations. Second, they found that one-half of the low glucose concentrations were measured in the first 6 hours after birth, confirming the previously described nadir in glucose concentrations. Third, they found that 37% of patients with a documented low glucose had their first episode after 3 normal glucose measurements and 6% had their first episode after 24 hours. Finally, the incidence of low glucose concentrations was higher in the current study compared with other studies of the same patient populations.[11,13–15] Reasons for this discrepancy may include the more standardized approach to timing of collection and processing of blood samples, as well as initial use of the more accurate glucose oxidase method for measurement. Another reason for the higher incidence is the higher threshold Harris et al used to define a low concentration in the current study compared with other studies.

Do the findings in the Harris study mean that we should use 2.6 mM as a cut-off for further action in an asymptomatic but at risk patient, no matter how old they are? Or should the lower and age specific cut-offs in the AAP guidelines be used? Should we continue screening all asymptomatic infants beyond 3 normal measurements and through 48 hours? For the sake of simplicity, should we apply the same set of guidelines to each of these populations? The answers to these questions will continue to be argued and the data provided by Harris et al will be used to support all sides of the debate. What is clear is that the higher one's glucose threshold and the more often one tests for it, the more often asymptomatic patients with low glucose concentrations will be identified. What clinicians will do with this information will depend on how they view any particular glucose concentration in an asymptomatic newborn. Is there immediate harm from this concentration, is it a harbinger of persistent and/or more severe low glucose concentrations, which may go on to cause harm? Or is this concentration simply part of the lower end of "normal" neonatal transition? The study by Harris et al does not answer these questions, because it was designed to be an observational study to measure the incidence of glucose concentrations <2.6 mM among the 4 populations of neonates, not to focus on outcomes of different definitions of "hypoglycemia" or outcomes of treatment or no treatment.

To answer these questions an interventional trial comparing treatments at 2 different glucose concentration thresholds with long-term neurodevelopmental follow-up might be performed. What would the ideal trial look like? What concentrations would be tested, what treatment algorithm would be used, how would a clinically significant outcome be defined and tested for and at what age(s), and how many patients would be required? Such essential questions have been thoughtfully addressed in a review by Boluyt et al in which they present one strategy for executing this type of study.[9] Is there enough debate over this issue that equipoise can be reached for an interventional trial? Or will debate, which has been a hallmark of this field for decades, simply lead to further guidelines based on current (meaning past) data in the literature?

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Glossary

AAP	American Academy of Pediatrics
IDM	Infants of diabetic mothers

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