EDITORIAL

Hypoglycemia in the Newborn and Neurodevelopmental Outcomes in Childhood

Paul J. Rozance, MD

Hypoglycemia is a common condition in newborns, and its management is a frequently debated topic in pediatrics and neonatology. Some newborns with hypoglycemia have permanent brain injury, especially infants with persistent genetic hypoglycemia disorders such as congenital hyperinsulinism. Brain injury also can occur in newborns without identified genetic hypoglycemia disorders, particularly if the hypoglycemia persists for many hours to days and is associated with signs of acute brain dysfunction, such as lethargy, coma, and seizures. In addition, the inability to predict which newborns will have brain injury based on the glucose concentration, the duration of hypoglycemia, and associated signs complicates management.[1] Even the question of whether asymptomatic or mildly symptomatic hypoglycemia in genetically normal newborns can cause brain injury is unanswered. Often, the same features that increase the risk of hypoglycemia in newborns also increase the risk for poor outcomes independent of hypoglycemia.[1] Two studies in this issue of *JAMA* provide new findings that inform how neonatal hypoglycemia can be understood and managed.

Related articles pages 1149 and 1158

In one of the articles in this issue of *JAMA*, Shah and colleagues[2] report educational achievement among 480 children in the Children With Hypoglycaemia and Their Later Development (CHYLD) cohort, which is one of the most important cohorts in which the association between neonatal hypoglycemia and poor outcomes has been examined. Almost all newborns recruited had at least 1 of the common risk factors for asymptomatic neonatal hypoglycemia: a mother with diabetes, preterm birth (<37 weeks' gestation), or small (<10th percentile or <2500 g) or large (>90th percentile or >4500 g) for gestational age. Newborns with inherited metabolic disorders or hyperinsulinism were excluded. Infants were tested for hypoglycemia using highly accurate glucometers that report plasma equivalent glucose concentrations. Hypoglycemia was defined as a glucose level less than 47 mg/dL and was treated with feeding, dextrose gel, or intravenous dextrose to achieve glucose concentrations of 47 mg/dL or higher. While this management strategy is consistent with World Health Organization recommendations, it is not universally recommended.[3,4]

In the current study, the authors report outcomes among the children at 9 to 10 years of age, along with numerous secondary outcomes related to executive function, visual-motor function, psychosocial adaptation, and general health. The investigators found that newborns exposed to neonatal hypoglycemia did not have significantly different rates of low educational achievement (defined as performing below normative curriculum level in standardized tests of reading comprehension or mathematics) compared with infants without exposure (47% vs 48%; adjusted risk difference, −2% [95% CI, −11% to 8%]; adjusted risk ratio, 0.95 [95% CI, 0.78 to 1.15]). In previous studies from this same cohort, assessment at age 2 years demonstrated that neonatal hypoglycemia was not associated with adverse outcomes,[5] but at 4.5 years, there was an increased risk of low executive function and visual-motor impairment in hypoglycemic newborns.[6] Concern that low executive function and visual-motor impairment may have impaired academic performance as the children aged was not confirmed in the current study.

This study was not a randomized clinical trial that tested the efficacy of a particular hypoglycemia management strategy. In addition, given that 48% of children without exposure to hypoglycemia demonstrated low educational achievement, over twice as high as rates expected by the investigators, further research aimed at defining an optimal management strategy is warranted. The findings also suggest that antenatal conditions that are associated with increased risk of hypoglycemia among newborns are associated with increased risk for impaired neurodevelopment and educational achievement, independent of neonatal hypoglycemia.

The results reported by Shah and colleagues[2] contrast with a previous study by Kaiser et al[7] that found an association between early transient hypoglycemia and lower academic achievement at 10 years of age. The previous study included 1395 newborns and focused on early and transient hypoglycemia, not ongoing hypoglycemia as in the current cohort, and raised the possibility that management strategies identify hypoglycemia too late for effective intervention. Another study in this issue of *JAMA* by Edwards and colleagues[8] addresses this possibility. The investigators tested the effect of prophylactic dextrose gel administered to newborns with the first feed on 2-year developmental outcomes. Dextrose gel is an accepted treatment for neonatal hypoglycemia and, given the associations identified in the previous study by Kaiser et al,[7] consideration of dextrose gel to prevent neonatal hypoglycemia is warranted.

The study by Edwards and colleagues[8] was a double-blind, randomized, multicenter clinical trial that included 2149 newborns and was conducted in Australia and New Zealand. The inclusion criteria were similar to the CHYLD cohort, although newborns were excluded if they had a birthweight less than 2.2 kg, a gestational age less than 35 weeks, or had an indication for neonatal intensive care unit admission. Previously reported short-term outcomes from this

trial demonstrated that prophylactic dextrose gel was more effective than placebo in preventing hypoglycemia (glucose level <47 mg/dL; 37% vs 42%).[9] Only the subset of infants who resided in New Zealand (n = 1197) were included in the current study; the authors report that for logistical reasons, including COVID-19 restrictions, follow-up of infants randomized in Australia was not possible.

The investigators found that the primary outcome of neurosensory impairment at 2 years' corrected age was not significantly different between the prophylactic dextrose gel and placebo groups (20.8% vs 18.7%; risk difference, 2.09% [95% CI, −2.43% to 6.60%]; adjusted risk ratio, 1.13 [95% CI, 0.90 to 1.41]). However, some secondary outcomes were worse among infants in the prophylactic dextrose gel group, including lower Bayley-III composite scores for cognitive, language, and motor function as well as a higher risk of motor delay. Additionally, the 95% CI for the primary outcome of neurosensory impairment included up to a 7% increased risk for neurosensory impairment in the prophylactic dextrose gel group. The 7% increased risk was defined by the investigators as potentially clinically important, and the study may have been underpowered to detect small differences in the primary outcome.

The reasons children who received prophylactic dextrose gel would have adverse outcomes is unclear. One potential reason explored by the investigators is that prophylactic dextrose gel may have caused the diagnosis of hypoglycemia to be delayed or missed in some infants, thus delaying or preventing definitive treatment. While this possibility cannot be totally excluded, there was no difference between the groups with respect to the proportion of infants ultimately treated for hypoglycemia or the number of blood tests performed, making this explanation unlikely. Furthermore, a smaller preliminary study (involving 360 newborns with hypoglycemia) that tested the effect of different prophylactic dextrose gel doses compared with placebo did not find significant differences in outcomes at 2 years.[10] Based on the results of these 2 prophylactic dextrose gel studies, the conclusion should not be that prophylactic dextrose gel caused the adverse outcomes. However, incorporation of prophylactic dextrose gel into clinical practice should await further research.

Longer-term outcome data from the current trial by Edwards et al,[8] studies of prophylactic dextrose gel in other cohorts, and further clinical trials will be helpful to inform clinical questions about management of hypoglycemia in newborns. An ideal study would randomize newborns with hypoglycemia to treatment or no treatment, although equipoise and ethical support for such a study are lacking. Another strategy would be to randomize newborns with hypoglycemia to receive low or high treatment glucose concentration goals.[11] A study that used this approach among 582 newborns found no differences in 18-month psychomotor development between the 2 groups.[12] Although this seems to favor the idea that neonatal hypoglycemia does not cause poor outcomes, the study design excluded newborns with an initial glucose concentration of 35 mg/dL or less, the very patients who may be at most risk for impaired neurodevelopment.

Another potential strategy is to randomize newborns with hypoglycemia to a placebo-controlled delay in treatment. A previous study of 237 newborns did use this strategy,[13] and despite demonstrated benefit of dextrose gel for treating hypoglycemia, 2-year outcomes (including neurologic function; executive function; and cognitive, language, behavior, and motor skills) were not different.[14] The study by Edwards and colleagues[8] also can be viewed as a trial of delayed treatment. However, given the difference in rates of hypoglycemia and the first glucose concentrations in the 2 groups (56.9 mg/dL and 53.5 mg/dL in the dextrose and placebo gel groups, respectively[9]), detecting a difference in 2-year outcomes perhaps was unlikely. Furthermore, while 2-year outcome data are important to demonstrate safety, outcomes at older ages, when executive function and academic achievement can be assessed, will be important when considering the effect of neonatal hypoglycemia and its management.

Whether the relationship between hypoglycemia and impaired neurodevelopment is causative or an association remains to be determined. However, the reports by Shah et al[2] and Edwards et al[8] in this issue of *JAMA* provide important new data about the clinical importance and management of neonatal hypoglycemia and subsequent neurodevelopmental outcomes.

ARTICLE INFORMATION

Author Affiliation: Perinatal Research Center, University of Colorado, School of Medicine, Aurora.

Corresponding Author: Paul J. Rozance, MD, University of Colorado School of Medicine, Perinatal Research Center, 13243 E 23rd Ave, MS F441, Aurora, CO 80045 (paul.rozance@cuanschutz.edu).

Conflict of Interest Disclosures: Dr Rozance reported receiving a Nova StatStrip for use in his laboratory from Nova Biomedical.

REFERENCES

1. Rozance PJ, Hay WW. Hypoglycemia in newborn infants: features associated with adverse outcomes. *Biol Neonate*. 2006;90(2):74-86. doi:10.1159/000091948

2. Shah R, Dai DWT, Alsweiler JM, et al; Children With Hypoglycaemia and Their Later Development (CHYLD) Study Team. Association of neonatal hypoglycemia with academic performance in mid-childhood. *JAMA*. Published March 22, 2022. doi:10.1001/jama.2022.0992

3. Thornton PS, Stanley CA, De Leon DD, et al; Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *J Pediatr*. 2015;167(2):238-245. doi:10.1016/j.jpeds.2015.03.057

4. Adamkin DH; Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127(3):575-579. doi:10.1542/peds.2010-3851

5. McKinlay CJ, Alsweiler JM, Ansell JM, et al; CHYLD Study Group. Neonatal glycemia and neurodevelopmental outcomes at 2 years. *N Engl J Med*. 2015;373(16):1507-1518. doi:10.1056/NEJMoa1504909

6. McKinlay CJD, Alsweiler JM, Anstice NS, et al; Children With Hypoglycemia and Their Later Development (CHYLD) Study Team. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. *JAMA Pediatr*. 2017;171(10):972-983. doi:10.1001/jamapediatrics.2017.1579

7. Kaiser JR, Bai S, Gibson N, et al. Association between transient newborn hypoglycemia and fourth-grade achievement test proficiency: a population-based study. *JAMA Pediatr*. 2015;169(10):913-921. doi:10.1001/jamapediatrics.2015.1631

8. Edwards T, Alsweiler JM, Crowther CA, et al. Prophylactic oral dextrose gel and neurosensory impairment at 2-year follow-up of participants in

the hPOD randomized trial. *JAMA*. Published March 22, 2022. doi:10.1001/jama.2022.2363

9. Harding JE, Hegarty JE, Crowther CA, Edlin RP, Gamble GD, Alsweiler JM; hPOD Study Group. Evaluation of oral dextrose gel for prevention of neonatal hypoglycemia (hPOD): a multicenter, double-blind randomized controlled trial. *PLoS Med*. 2021;18(1):e1003411. doi:10.1371/journal.pmed.1003411

10. Griffith R, Hegarty JE, Alsweiler JM, et al. Two-year outcomes after dextrose gel prophylaxis for neonatal hypoglycaemia. *Arch Dis Child Fetal Neonatal Ed*. 2021;106(3):278-285. doi:10.1136/archdischild-2020-320305

11. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. *Pediatrics*. 2006;117(6):2231-2243. doi:10.1542/peds.2005-1919

12. van Kempen AAMW, Eskes PF, Nuytemans DHGM, et al; HypoEXIT Study Group. Lower versus traditional treatment threshold for neonatal hypoglycemia. *N Engl J Med*. 2020;382(6):534-544. doi:10.1056/NEJMoa1905593

13. Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;382(9910):2077-2083. doi:10.1016/S0140-6736(13)61645-1

14. Harris DL, Alsweiler JM, Ansell JM, et al; Children with Hypoglycaemia and their Later Development (CHYLD) Study Team. Outcome at 2 years after dextrose gel treatment for neonatal hypoglycemia: follow-up of a randomized trial. *J Pediatr*. 2016;170:54-9.e1, 2. doi:10.1016/j.jpeds.2015.10.066