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Review

Neonatal hypoglycemia

David H. Adamkin*

Division of Neonatal Medicine, Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY, USA

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SUMMARY

A consistent definition for neonatal hypoglycemia in the first 48 h of life continues to elude us. Enhanced understanding of metabolic disturbances and genetic disorders that underlie alterations in postnatal glucose homeostasis has added useful information to understanding transitional hypoglycemia. This growth in knowledge still has not led to what we need to know: "How low is too low and for how long?" This article reviews the current state of understanding of neonatal hypoglycemia and how different approaches reach different "expert" opinions.

1. Introduction

Management of low glucose concentrations in the first 48 h of life is one of the most frequently encountered issues in newborn care. The levels used to make decisions remain more a matter of expert opinion than based on evidence. The data needed to establish agreement on levels to treat have not been definitive enough to gain consensus. Recently a number of studies as well as position papers from two pediatric organizations have provided some new substance for debate and suggest that the design of studies may move toward a more evidence-based approach to neonatal hypoglycemia [1,2].

More than 50 years ago, Marvin Cornblath recognized that low blood glucose levels in small for gestational age (SGA) and preterm infants were associated with seizures [3]. It became clear that symptomatic hypoglycemia could lead to long-term neurologic deficits. However, the definition of clinically significant hypoglycemia still eludes us. Therefore, we still have limited evidence-based consensus regarding the screening and management of infants at risk for hypoglycemia. While there is agreement that recurrent severe hypoglycemia causes brain injury, there are now more recent studies fueling the debate about the relationship of neurodevelopmental outcomes and transient neonatal hypoglycemia [4,5].

The American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (COFN) recently ratified for another five years their statement on postnatal glucose homeostasis including an algorithm for screening and management of low glucose levels (Fig. 1) [1]. Also, recommendations and a re-evaluation of transitional hypoglycemia has been published by the Pediatric Endocrine Society (PES) [2,6]. A recent editorial called "Imperfect Advice" contrasts the two organizations' approaches and offers suggestions to merge both [7]. The purpose of this review is to evaluate the approaches taken by the two organizations and combine advice for management of low glucose levels over the first 48 h and how to diagnose potential cases of persistent hypoglycemia prior to discharge. The review includes a discussion of postnatal glucose homeostasis including transitional hypoglycemia. This is followed by a discussion contrasting neuroendocrine and metabolic data versus individual risk assessment, examination of the infant and corroboration of these levels with neurodevelopmental outcome data to reach recommendations for action.

2. Postnatal glucose homeostasis

At birth, the infant's blood glucose concentration is about 70% of the maternal level. It falls rapidly to a nadir by 1 h to a value as low as 20–25 mg/dL [8]. This nadir and the lower levels are prevalent in healthy neonates and are seen in all mammalian newborns. These levels are transient and begin to rise over the first hours and days of life. This observation is considered to be part of the normal adaptation for postnatal life that helps establish postnatal glucose homeostasis [8–10]. Are there advantages to having a lower blood glucose concentration compared with adults for the first two days of life? A decrease in glucose concentration soon after birth might be essential to stimulate physiological processes that are required for postnatal survival, including promoting glucose production

* Address: Division of Neonatal Medicine, Department of Pediatrics, University of Louisville School of Medicine, 571 S. Floyd St., Suite 342, Louisville, KY 40202-3830, USA. Tel.: +44 502 852 8470.
E-mail address: david.adamkin@louisville.edu.

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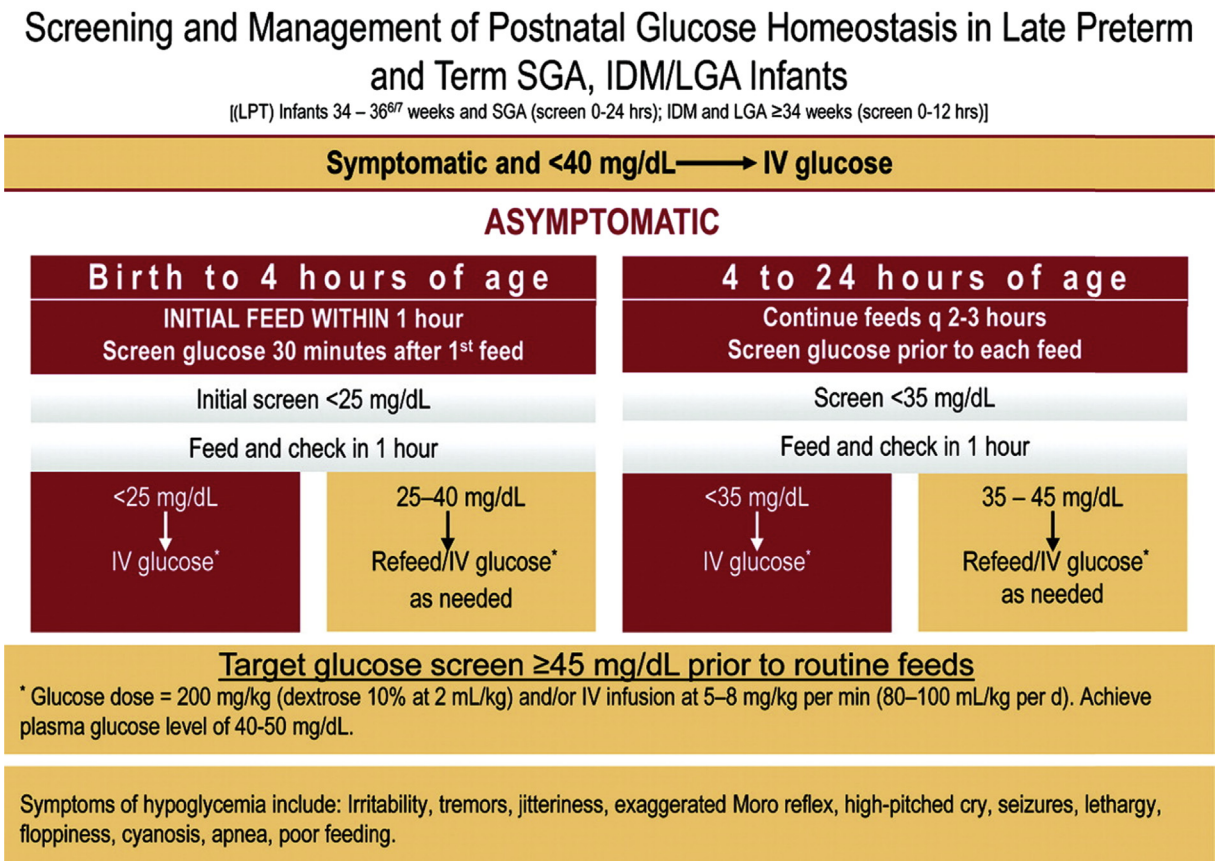

Fig. 1. Screening for and management of postnatal glucose homeostasis in late preterm (LPT 34–$36^{6/7}$ weeks) and term small for gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large for gestational age (LGA) infants. LPT and SGA (screen 0–24 h), IDM and LGA ≥34 weeks (screen 0–12 h). IV, intravenous. Reproduced with permission from Adamkin [1].

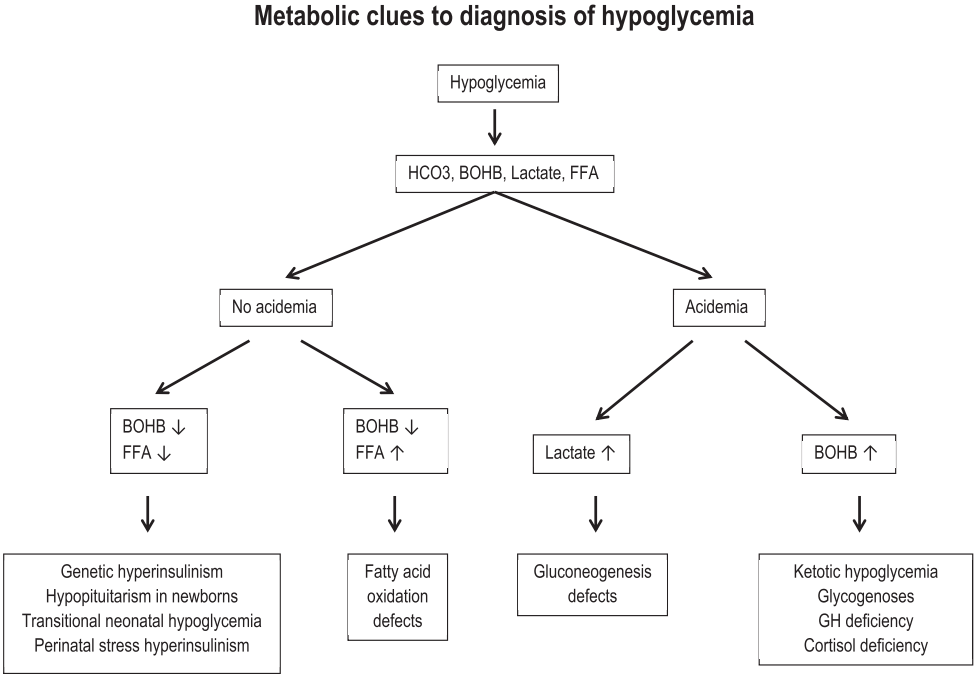

Fig. 2. Algorithm showing how the major categories of hypoglycemia may be determined with information from the critical sample. BOHB, beta-hydroxybutyrate; FFA, free fatty acids; GH, growth hormone. Reproduced with permission from Thornton et al. [2].

through gluconeogenesis and glycogenolysis [11]. In addition, the decrease in glucose concentration enhances oxidative fat metabolism, stimulates appetite, and may help adapt to fast-feed cycles [11]. Persistently lower glucose concentrations might be the result of mechanisms that were vital for the fetus to allow maternal-to-fetal glucose transport but not reversed after birth [11]. However, these lower levels may also be associated with peripartum stress (fetal distress, birth asphyxia, or low Apgar scores) and with low weight-for-length ratios, consistent with fetal growth restriction [12,13]. Perinatal stress is now recognized as associated with hyperinsulinemic hypoglycemia that may continue until several weeks of age [12,13]. Therefore, if these low levels persist over the first hours and days of life then the diagnosis of persistent stress hyperinsulinism must be considered and evaluated to prevent the discharge of an infant with a persistent hypoglycemic syndrome. Figure 2 shows the metabolic clues to arriving at this diagnosis [2]. Measurement of beta-hydroxybutyrate, free fatty acids, and lactate at the time of a hypoglycemic episode provides important information for diagnosing the cause of hypoglycemia [2].

The PES increases the risk categories (Box 1) from the AAP document from late preterm and term SGA, large for gestational age (LGA), and infants of diabetic mothers (IDM) infants to also include perinatal stress (birth asphyxia, ischemia, cesarean sections for fetal distress), maternal pre-eclampsia /eclampsia or hypertension, meconium aspiration syndrome, erythroblastosis fetalis, premature or post-mature delivery. Also, infants with a family history of a genetic form of hypoglycemia and congenital syndromes such as Beckwith–Wiedeman and neonates with abnormal physical findings (e.g. midline facial malformations, microphallus) would be screened [2].

Box 1
Recognizing and managing neonates at increased risk for a persistent hypoglycemia disorder.

Neonates at increased risk of hypoglycemia and require glucose screening:

1. Symptoms of hypoglycemia.
2. Large for gestational age (even without maternal diabetes).
3. Perinatal stress:
   (a) birth asphyxia/ischemia; cesarean delivery for fetal distress;
   (b) maternal pre-eclampsia/eclampsia or hypertension;
   (c) intrauterine growth restriction (small for gestational age);
   (d) meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia.
4. Premature or post-mature delivery.
5. Infant of diabetic mother.
6. Family history of a genetic form of hypoglycemia.
7. Congenital syndrome (e.g. Beckwith–Wiedemann), abnormal physical features (e.g. midline facial malformations, microphallus).

Neonates in whom to exclude persistent hypoglycemia before discharge:

1. Severe hypoglycemia (e.g. episodes of symptomatic hypoglycemia or need for intravenous dextrose to treat hypoglycemia).
2. Inability to consistently maintain preprandial PG concentration >50 mg/dL up to 48 h of age and >60 mg/dL after 48 h of age.
3. Family history of genetic form of hypoglycemia.

Reproduced with permission from Thorton, et al. [2].

3. Screening for low glucose levels

A study by Harris and colleagues used a value of <47 mg/dL to define hypoglycemia in the first 48 h of life for the four at-risk populations of neonates used in the AAP document and algorithm. They found that 25% of all deliveries were at risk and 51% of these four at-risk groups had at least one blood glucose concentration <47 mg/dL [14]. This study used glucose oxidase method for the initial sampling as opposed to the less precise “bedside” screening method. Therefore, applying this value to screening merely these four groups means that in the USA, more than 550,000 neonates would be screened and 12.5% of all newborns would be diagnosed with hypoglycemia.

What is clear from this study is that the higher an individual's glucose threshold is for screening and the more often these tests are performed, the more often asymptomatic patients with low blood glucose will be identified [11]. If we define and screen more at-risk groups, it adds to the next variable which is: what does the individual clinician do with this information in an asymptomatic infant?

4. Transitional neonatal hypoglycemia

Using neuroendocrine and metabolic data, the Pediatric Endocrine Society re-evaluated the brief period of hypoglycemia that occurs in the first 48 h of life called transitional neonatal hypoglycemia [6]. This period is characterized by a relative hyperinsulinism, low ketone levels, inappropriate preservation of glycogen, and mean glucose levels of 55–65 mg/dL [6]. This period and these data resemble a known form of congenital hyperinsulinism, causing a lowering of the plasma glucose threshold for suppression of insulin secretion [2]. The 55–65 mg/dL range is the same level below which adults and older children demonstrate neurogenic symptoms; therefore the PES interpretation was that this neuroendocrinologic and metabolic profile suggests activated mechanisms for brain protection and is the critical range of glucose maintenance the first 48 h of life [2]. By 72 h of life, glucose levels rise to those observed in older children and adults (>70 mg/dL) [2,6]. Two important distinctions by the PES versus the AAP include the focus on mean glucose levels by the PES and the interpretation of the endocrine and metabolic data that this period was characterized by an absence of alternative fuels [6]. The AAP guideline used the lower ranges of glucose concentrations found in the fetus and asymptomatic infants and relies on clinical status [7,8]. Using the endocrine-based mechanisms for determining critical levels of glucose, hyperinsulinemia accompanied by suppressed levels of ketones [9] and inappropriately large glycemic responses to glucagon and epinephrine [10], suggest the absence of alternative fuels and the inappropriate preservation of glycogen in a newborn with low glucose levels, all consistent with a hypoketotic hyperinsulinemia [2].

The AAP algorithm during the first hours of transition uses lower ranges of glucose values from fetal and neonatal data [8,15]. The COFN disagreed that the rise in ketones after 24 h represented caloric deprivation instead of an association with breastfeeding and ketones as an alternative energy source, as these infants tend to have lower levels of plasma glucose than those that are formula-fed [16].

5. Screening levels in the AAP document

The lowest acceptable level of glucose in the AAP algorithm is 25 mg/dL after the first feedings with actionable levels between 25 and 40 mg/dL during the first 4 h of life or during transition after birth [1]. These levels approximate epidemiologic data at the fifth to tenth percentile for glucose. From 4 to 24 h, the lowest level for action is 35 mg/dL and then the actionable range is 35–45 mg/dL [1]. The PES recommendations review interesting data from a time when newborns were fasted between 8 and 24 h in the 1950s and 60s showing that mean glucose levels were remarkably stable and relatively unaffected by timing of feeding and feeding interval. For example, the 8 h fast resulted in a mean plasma glucose level in normal newborn infants of 57–69 mg/dL [17]. Data from breastfeeding term, appropriate for gestational age infants on contemporary feeding patterns (with no fasting) revealed a range of plasma glucose levels from 25 to 144 mg/dL over the first 72 h of life and an interquartile range of 41–60 mg/dL [18]. Therefore, the majority of the interquartile range for breastfeeding, well babies with no risk factors, is below the 55–65 mg/dL threshold related to the endocrine and metabolic profile for the first 48 h of life. Feeding initiation and interval are very important at the lower levels of plasma glucose. Early feeding initiation is critical to establish the benefits of breastfeeding and to maintain plasma glucose levels [1].

6. Neurodevelopmental outcome

The neurodevelopmental outcome approach is to find the critical threshold of plasma glucose associated with brain injury or where "neuroglycopenia" occurs in the newborn. In the adult, this is 50 mg/dL. This research was profoundly influenced by a multicenter nutrition study from the UK published in 1988 [19]. Neuroglycopenia is the level at which there is an inadequate supply of glucose for the brain. The authors of the study suggested that they had found the critical glucose concentration, <47 mg/dL, that would reliably predict adverse outcomes [19]. The study evaluated blood glucose levels, drawn daily initially then weekly, until discharge on 661 infants <1850 g at birth who were enrolled in a nutrition study looking at early diets and cognitive outcomes. They found that the number of days on which these infants experienced moderate hypoglycemia (<47 mg/dL) was strongly related to reduced scores for mental and motor development at 18 months of corrected age, even after adjustment for a wide range of factors known to influence development [19]. One study weakness was that the study group included sicker infants who had more frequent determinations of blood glucose. Hypoglycemia was not the focus of this prospective controlled feeding trial, but it becomes apparent from the observations that some infants were permitted to have plasma glucose levels <20 mg/dL for as long as 3–7 days without intervention. Only the first glucose value of the day was used in the data analyses. The investigators found that a first glucose value <47 mg/dL in high risk infants with birthweight <1850 g on five or more days correlated positively with abnormal neurologic and developmental outcomes at 18 months of age [19]. This value of "47" mg/dL became the worldwide standard and was applied even to term appropriate for gestational age (AGA) healthy neonates as the gold standard "critical threshold" defining hypoglycemia and risk of brain injury. However, lesser differences were found when the children were seen again as part of a larger study when the children were 7–8 years of age [20]. The authors themselves suggested in a later letter that there is "difficulty of providing causation when an observational approach is used," and remarked that "when such observations generate hypotheses or legitimate clinical concerns, this should stimulate future studies and randomized controlled trials" [21].

A study almost 25 years later from the UK conducted a prospective trial including infants <32 weeks of gestation who had blood glucose levels measured daily for the first 10 days of life. Forty-seven of the 566 who survived to 2 years of age had a blood glucose level <47 mg/dL on at least three days of the first 10 days of life [22]. All were matched for appropriate variables with hypoglycemia-free controls. No differences were found in developmental progress or physical disability at 2 years of age [22]. Remarkably, with 81% of the original cohort matched again at 15 years of age, they were almost identical in full scale IQ. The inclusion of children who had a level <47 mg/dL for >4 days and another group <37 mg/dL on three different days did not alter these results [22]. The authors concluded that "they found no evidence that recurrent low blood glucose levels (<47 mg/dL) in the first 10 days of life pose a hazard to preterm infants." The study does not imply that low blood glucose levels cannot be damaging in the preterm infant even in the absence of clinical signs. However, the data suggest that the danger threshold must be lower than many had come to think it was.

By contrast, a retrospective study from the Netherlands examined infants at $32–35^{6/7}$ weeks of gestational age whose parents completed the Ages and Stages Questionnaire. They found that at 4 years of age, the odds of normal development were reduced by more than 50% in children with at least one glucose level <30 mg/dL in the first 72 h of life [4]. No other neonatal morbidity (e.g. Apgar scores, asphyxia, septicemia, mechanical ventilation, or hyperbilirubinemia) was associated with developmental delay [4]. Only hypoglycemia, <30 mg/dL in moderately preterm infants, was associated in a parent-reported developmental delay report at preschool age. A glucose value <30 mg/dL was widespread (8.1% had such a level), and was associated with 9–20% increased risk of developmental delay [4]. These children did not have physician-mediated neuropsychological testing. This and the absence of poor outcome with any other morbidity contrasts with other studies linking glucose levels and neurodevelopmental outcome.

In a unique study from Arkansas, investigators evaluated 1400 infants at 10 years of age who had a single glucose level in the first hours of life <30–45 mg/dL [5]. On the basis of fourth-grade school examinations from across the state, they found that a single episode of hypoglycemia, defined as <40 mg/dL that resolved by 3 h of age, was associated with a 50% reduction in the odds of achieving proficiency in literacy and numeracy [5]. This group of patients represented all of the deliveries during a calendar year, so they were mostly made up of late preterm and term infants. Their low glucose levels were followed by a second value above the cut-off of <30, <40, and <45 mg/dL, respectively. Little information was supplied about how the low glucose levels were managed and there was no information about the rate of breastfeeding, both of which may be confounders [23]. It is not certain whether the exposure group had only the one episode of hypoglycemia, since no values were reported after the second value. The possibility of residual confounding remains in the study despite extensive adjustment for perinatal and socio-economic factors [24]. As yet, there is no reason to assume that the link between transitional neonatal hypoglycemia and subsequent poor academic performance is causal. It is possible that a brief period of hypoglycemia is a marker for other perinatal issues perhaps including events during intrauterine development.

Current guidelines recommend screening only for newborns that are symptomatic or at risk of developing hypoglycemia. The Arkansas study suggests that transient newborn hypoglycemia may be associated with poorer academic achievement at age 10 years. Should we now consider universal glucose screening of all neonates? Screening is only justified when you can impact outcome with the result of the screen. The brief period of "hypoglycemia" was diagnosed at 90 min of age but the actual result was available 30 min after that. The second measurement showing resolution

above the threshold came 70 min after the first screen, or at ~3 h of age. It is unlikely that any intervention after the results are known could shorten the exposure to the brief period of "hypoglycemia."

Studies from The Children with Hypoglycemia and their Later Development studies (CHYLD) have added new information about the effects of neonatal hypoglycemia and developmental outcomes. The investigators report on 614 term and late preterm infants at risk for hypoglycemia using the same categories as the AAP guidelines [1,25]. This study also included continuous interstitial glucose monitoring that did not influence clinical care, as it was masked from the clinicians. The patients studied included those without hypoglycemia, and both treated and untreated hypoglycemic infants [25]. Hypoglycemia was defined as plasma glucose <47 mg/dL.

The infants were screened and treated with the aim of keeping concentrations of plasma glucose >47 mg/dL. Surprisingly, there were long and undetected periods of hypoglycemia detected only on interstitial monitoring. Additionally, high or "unstable" glucose concentrations (>54–72 mg/dL) were associated with worse developmental outcomes. Therefore, a U-shaped curve of potential morbidity emerges with both low glucose levels and modestly elevated plasma glucose levels [24]. More than half of the infants at risk were diagnosed with hypoglycemia. Almost one out of four had hypoglycemic episodes not detected with intermittent blood sampling [25]. Twenty-five percent of those undetected episodes lasted >5 h during the first week of life [25].

Neurosensory impairment or processing difficulty at age 2 years reported among five groupings, including a reference group who never had a level <47 mg/dL, any episode of hypoglycemia, >3 days of hypoglycemia, or severe hypoglycemia, respectively [25]. There was no association between neonatal hypoglycemia and neurodevelopmental outcome at age 2 years. The authors also looked at the relationship between silent episodes not detected on intermittent blood sampling and outcome at age 2 years. They compared 108 patients with no events versus 33 who had at least one or more episodes <47 mg/dL and showed no difference in neurosensory impairment or processing difficulty [25]. However, data on the 4.5-year follow-up demonstrated executive function difficulties in those infants suffering more than one episode of hypoglycemia, found only with the continuous glucose monitoring [25]. This study from Harris et al. adds another modality for the management of asymptomatic neonatal hypoglycemia [6].

This next study from the CHYLD was a follow-up of 184 children with hypoglycemia defined as glucose <47 mg/dL in the first 48 h of life [26]. Patients were randomized to either dextrose or placebo gel (Sugar Babies Study). The infants had the same risk categories as the AAP guideline and were followed over the first 48 h with aggressive treatment to maintain plasma glucose levels >47 mg/dL.

Using this threshold, half of the "at-risk" infants were diagnosed as having neonatal hypoglycemia. Feedings were encouraged and those for whom poor feeding was an issue were given expressed breast milk or formula by syringe. The primary outcome of the study was treatment failure, defined as a plasma glucose concentration <47 mg/dL despite two treatment attempts with the dextrose gel [26]. The study also assessed both visual global motion perception and executive function into a single measure that they called processing difficulty [26]. Both of these assessments target cortical networks that may be susceptible to neonatal hypoglycemia.

Magnetic resonance imaging of the brain in humans suggests that the occipital lobe may be vulnerable to injury caused by neonatal hypoglycemia, and a link between hypoglycemia and visual impairment has been previously reported [27,28]. They were especially interested in the visual global perception because it involves extrastriate visual areas within the dorsal visual cortical processing stream, which emanates from the occipital lobe [29]. Executive function is a collective term for the skills required to learn and interact with the environment, including working memory, reasoning, task flexibility, and problem solving. These skills involve a network of areas within the brain [24].

The neurodevelopmental outcomes at age 2 years were available for 78% of the original hypoglycemic cohort. Rates of neurosensory impairment, processing difficulties, and multiple secondary growth and developmental outcomes were equivalent between the dextrose gel and placebo groups. The rate of neurosensory impairment at age 2 years was high at 35% for both controls and dextrose gel-treated infants [26]. Most of the neurosensory impairment was mild and an overlapping cohort study with hypoglycemia treated at <47 mg/dL was not associated with increased risk of impairment compared with at-risk patients without hypoglycemia [25].

Even though Sugar Babies had a "negative" result, the study is very useful for health care providers. Short term outcomes for the at-risk patients showed significant benefit of the dextrose gel as a treatment for asymptomatic hypoglycemia [26]. Infants randomized to dextrose gel had significantly less treatment failure, defined as a glucose <47 mg/dL after two treatment attempts with the dextrose gel or placebo. Treatment with the dextrose gel also lowered rates of neonatal intensive care admissions for hypoglycemia, with a number needed to treat of 8. Rebound hypoglycemia (within 6 h: 12%) and recurrent hypoglycemia (within 48 h of birth: 24%) were similar between groups [26].

The gel appears to be safe and may reduce risks related to treatment of hypoglycemia, such as decreasing breastfeeding, and decreasing health care costs. The advantages of treatment with the gel do not place infant outcomes in jeopardy compared to more traditional treatment when seen in follow-up at age 2 years [26].

Another study including 75 healthy, term, LGA infants born to non-diabetic mothers had screening glucose levels at 1, 3, and 5 h after birth [30]. Intravenous glucose was provided for severe or symptomatic hypoglycemia. Development and behavior were examined at age 4 years. There were no significant differences between children with normoglycemia and hypoglycemia <40 mg/dL at 1 h or <45 mg/dL subsequently [26]. There were no differences in any of the test scores between hypoglycemic children who had and who had not been treated with intravenous glucose [26].

It seems clear that 47 mg/dL is not the critical threshold for injury from low glucose levels. In fact, a value <47 mg/dL is more important after 48 h than during the first 48 h. Continuous glucose monitoring shows that despite aggressive treatment, including treatment using the dextrose gel, infants identified with hypoglycemia experienced up to 5 h of hypoglycemia [25].

7. Summary

The optimal strategy for managing low plasma glucose levels in newborn infants remains elusive. Especially controversial is the most frequently occurring situation, namely the asymptomatic infant who is at risk with low plasma glucose levels. Numerous studies have shown that small for gestational age infants, infants of diabetic mothers, and late preterm infants have worse neurodevelopmental outcomes than healthy term infants [4,31–33]. In some of these groups, worse neurodevelopmental outcomes are associated with the presence of hypoglycemia [4,32]. However, no study has shown that preventing or treating the low plasma glucose level makes a difference in outcomes. We still do not know if the low glucose level is causal, is a surrogate for, or is augmenting, a different morbidity.

Recommendations from various organizations and experts are aimed at helping the clinician deal with low glucose levels after birth in normal newborns. The AAP guideline addressed only the first 24 h but we have added a recommendation for 24–28 h [1]. The PES recommendations were aimed at helping the clinician distinguish physiologically low levels of glucose in normal newborns from those that persist beyond 48 h of life. They also recommended the target threshold of >50 mg/dL for the first 48 h which differs from the AAP document [1,2]. The variability among the recommendations reflects the need for further research.

8. Recommendations for screening and management of hypoglycemia

At this time the following suggestions based on the aforementioned summarized data are offered [7]:

1. Use the AAP guidelines during the first 24 h of life to screen and manage glucose levels in high-risk, asymptomatic infants. This action is likely to provide a margin of safety and flexibility to identify those infants who require intravenous fluids and those with borderline levels that need to be followed beyond the first 48 h. This will promote successful breastfeeding and avoid unnecessary admission to the neonatal intensive care unit. The AAP guidelines do not address infants who are 24–48 h. We recommend that between 24 and 48 h, glucose levels should be >45 mg/dL.
2. On the basis of the current evidence, use of the AAP ranges for glucose screening and treatment of asymptomatic infants may reduce the chance of reaching higher glucose levels (as recommended by the PES) that may be associated with glucose instability and perhaps untoward neurodevelopmental outcome.
3. Consider delaying discharge from the nursery until the infants requiring intravenous glucose for symptomatic or asymptomatic low glucose levels or those with borderline glucose levels demonstrate glucose levels >70 mg/dL through several normal feed-fast cycles. More data on the frequency and success of diagnosing persistent hypoglycemia will be necessary to support this strategy.

Conflict of interest statement

None declared.

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References

[1] Adamkin DH, Committee on Fetus and Newborn. Clinical report – postnatal glucose homeostatsis in late-term and preterm infants. Pediatrics 2011;127:175.
[2] Thornton PS, Stanley CA, DeLeon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in neonates, infants, and children. J Pediatr 2015;167:238–45.
[3] Cornblath M, Odell GB, Levin E. Symptomatic neonatal hypoglycemia associated toxemia of pregnancy. J Pediatr 1959;55:545–62.
[4] Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF. Neonatal morbidities and developmental delay in moderately preterm born children. Pediatrics 2012;130:e265–72.
[5] Kaiser JR, Bai S, Gibson N, Holland G, Lin TM, Swearingen CJ, et al. Association between transient newborn hypoglycemia and fourth-grade achievement test proficiency: a population-based study. JAMA Pedatr 2015;169:913–21.
[6] Stanley C, Rozance P, Thornton MB, De Leon D, Harris D, Haymond MW, et al. Re-evaluating transitional neonatal hypoglycemia: mechanism and implications for management. J Pediatr 2015:1–6.
[7] Adamkin DH, Polin RA. Imperfect advice – neonatal hypoglycemia. J Pediatr 2016 Jun 10 [Epub ahead of print].
[8] Srinvasan G, Pildes RS, Cattamanchi G. Plasma glucose values in normal neonates: a new look. J Pediatr 1986;109:114–7.
[9] Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 h of life. J Pediatr 1987;110:119–22.
[10] Adamkin DH. Update on neonatal hypoglycemia. Archs Perinat Med 2005;11:13–5.
[11] Rozance P, Hay NW. Neonatal hypoglycemia answers but more questions. J Pediatr 2012;16:775–6.
[12] Collins JE, Leonard JV, Teale D, Marks V, Williams DM, Kennedy CR, et al. Hyperinsulinaemic hypoglycemia in small for dates babies. Archs Dis Childh 1990;65:1118–20.
[13] Hoe FM, Thornton PS, Wanner LA, Steinkrauss L, Simmons RA, Stanley CA. Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. J Pediatr 2006;148:207–12.
[14] Harris DL, Weston P, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr 2012;161:787–91.
[15] Marconi AM, Paolini C, Buscaglia M, Zerbe G, Battaglia FC, Pardi G. The impact of gestational age and fetal growth on the maternal–fetal glucose concentration difference. Obstet Gynecol 1996;87:937–42.
[16] Hoseth E, Joergensen A, Ebbesen F, Moeller M. Blood glucose levels in a population of healthy, breast fed, term infants of appropriate size for gestational age. Archs Dis Childh Fetal Neonatal Ed 2000;83:F117–9.
[17] Desmond MM, Hild JR, Gast JH. The glycemic response of the newborn infant to epinephrine administration: a preliminary report. J Pediatr 1950;37:341–50.
[18] Wight NE. Hypoglycemia in breastfed neonates. Breastfeed Med 2006;1:253–62.
[19] Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. Br Med J 1988;297:1304–8.
[20] Lucas A, Morley R, Cole TJ. Randomized trial of early diet in preterm babies and later intelligence quotient. BMJ 1998;318(7177):195.
[21] Lucas A, Morley R. Outcome of neonatal hypoglycemia [letter]. BMJ 1999;318(7177):195.
[22] Tin W, Brunskill G, Kelly T, Fritz S. 15 year follow-up of recurrent "hypoglycemia" in preterm infants. Pediatrics 2012;130:1497–503.
[23] McKinley CJ, Harding JE. Revisiting transitional hypoglycemia: only time will tell. JAMA Pediatrics 2015;169:892–4.
[24] McKinley CJD, Alsweiller JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015;373:1507–18.
[25] Harris DL, Alsweiler JM, Anssell JM, Gamble GD, Thompson B, Wouldes TA, et al. Outcomes at 2 years after dextrose gel treatment for neonatal hypoglycemia; follow-up of a randomized trial. J Pediatr 2016;170:54–9.
[26] Tam EW, Widjaja E, Blaser SI, MacGregor DL, Satodia P, Moore AM. Occipital lobe injury and cortical visual outcomes after neonatal hypoglycemia. Pediatrics 2008;122:507–12.
[27] Alkalay AL, Flores-Sarnat HB, Moser FG, Simmons CF. Brain imaging findings in neonatal hypoglycemia: case report and review of 23 cases. Pediatr (Phila) 2005;44:783–90.
[28] Braddick OJ, O'Brian JM, Wattam-Bell J, Atkinson J, Hartley T, Turner R. Brain areas sensitive to coherent visual motion. Perception 2001;30:61–72.
[29] Collette F, Van der Linden M. Brain imaging of the central executive component of working memory. Neurosci Biobehav Rev 2002;26:105–25.
[30] Brand PLP, Molenaar NLD, Kaaijk WS. Neurodevelopmental outcome of hypoglycemia in healthy, large for gestational age, term newborns. Archs Dis Childh 2005;90:78–81.
[31] Arcangeli T, Thilaganathan B, Hooper R, Khan KD, Bhide A. Neurodevelopmental delay in small babies at term: a systematic review. Ultrasound Obstet Gynecol 2012;40:267–75.
[32] Stenninger E, Flink R, Eriksson B, Sahlen C. Long-term neurological dysfunction and neonatal hypoglycemia after diabetic pregnancy. Archs Dis Childh Fetal Neonatal Ed 1998;79:F174–9.
[33] von Beckerath AK, Kollmann M, Rotky-Fast C, Karpf E, Lang U, Klaritsch P. Perinatal complications and long-term neurodevelopmental outcome of infants with intrauterine growth restriction. Am J Obstet Gynecol 2013;208:130–6.