REVIEW ARTICLE

Neonatal Hypoglycemia

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Abstract

Hypoglycemia is the most common metabolic problem in the neonatal period with a potential to cause brain injury. However, there are controversies in diagnosis, significance, and treatment of neonatal hypoglycemia. Several large-scale prospective and retrospective studies have reported the impact of neonatal hypoglycemia on neurodevelopment in high-risk infants. Significance of short-term hypoglycemia on neurodevelopment in healthy infants remains unresolved. There are also concerns that rapid correction of hypoglycemia may worsen brain injury. Conflicting recommendations from professional societies have further muddied the field. This review examines the current knowledge on the epidemiology of neonatal hypoglycemia, its impact on neurodevelopment, current screening and treatment recommendations, and the emerging role of dextrose gel for management of neonatal hypoglycemia.

Keywords: Hypoglycemia, Neonatology, Neurodevelopment, Newborn, Newborn infant, Preterm infants.

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Introduction

Hypoglycemia is a common metabolic problem in the neonatal period. Severe, prolonged, and recurrent hypoglycemia in the neonatal period is associated with brain injury. Several endocrine disorders and inborn errors of metabolism also present as neonatal hypoglycemia. A thorough understanding of neonatal hypoglycemia and its effects is necessary to prevent brain injury. However, there are controversies in the definition, significance, and treatment of neonatal hypoglycemia. Conflicting recommendations from professional societies have led to additional confusion. In the following sections I will review populations at risk for neonatal hypoglycemia, current knowledge on neurodevelopmental outcome after neonatal hypoglycemia, and commonly practiced screening and treatment strategies. Hypoglycemia due to congenital hyperinsulinism, endocrine disorders, and inborn errors of metabolism is not discussed.

Perinatal Glucose Metabolism

Prior to birth, the fetus is dependent on a continuous supply of glucose from the mother. Following the abrupt cessation of maternal glucose supply at birth, blood glucose levels decrease, reaching a nadir at around 2 hours of age.[1] Glucose levels normalize over the next several hours[2] due to a combination of feeding, glycogenolysis, and gluconeogenesis. The transient decrease in blood glucose occurs in all mammals and is probably essential for postnatal metabolic programming. In most infants, the transient decrease in blood glucose does not cause problems. However, under certain conditions it could lead to complications, including brain injury. The common causes of neonatal hypoglycemia are presented in Table 1. Hypoglycemia soon after birth is typically due to failure of metabolic adaptation or inadequate energy stores. Hyperinsulinism is the most common cause of persistent hypoglycemia beyond 24–48 hours of age.

Definition and Incidence

Definition of neonatal hypoglycemia has changed over time. A blood glucose concentration of <47 mg/dL (2.6 mmol/L) is commonly used at present. This value represents the 10th percentile blood glucose concentration in healthy full-term infants during the first 48 hours after birth.[2] A blood glucose concentration of <35 mg/dL (<2.0 mmol/L) is considered severe hypoglycemia. Using a blood glucose concentration <45 mg/dL (2.5 mmol/L) as definition, a study of approximately 2000 infants of 23 to 42 weeks gestation reported an 19% incidence of hypoglycemia in the first three hours after birth.[3] Severe hypoglycemia (blood glucose <35 mg/dL) was seen in 6%. Continuous glucose monitoring (CGM) detects more cases of hypoglycemia. Using a combination of CGM and intermittent plasma glucose measurements, Harris and colleagues found that 39% of healthy full-term infants have one or more episodes of blood glucose <47 mg/dL (<2.6 mmol/L) during the first five days after birth.[2] Incidence is higher in preterm infants, infants of diabetic mothers, small-for-gestation and large-for-gestation infants.[4,5] Standardized glucose monitoring of over 500 preterm, small-for-gestation and large-for-gestation infants, and infants of diabetic mothers during the first week after birth found a 51% incidence of hypoglycemia (<47 mg/dL [<2.6 mmol/L]) with no difference in incidence among the different risk groups.[4] The mean number of hypoglycemia episodes was one per infant (range: 1–7), and the mean duration was 1.4 hours (range: 0.2–4.5 hours). Most (81%) episodes occurred on the first day after birth. Nineteen percent had severe hypoglycemia (blood glucose <36 mg/dL [<2.0 mmol/L]) with 90% of cases occurring within 12 hours after birth. Recurrent hypoglycemia occurred in 19% with the majority (70%) occurring on day one.[4] Maternal obesity and cesarean section without labor have emerged as additional risk factors for neonatal hypoglycemia.[6]

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Table 1: Infants at risk for neonatal hypoglycemia

Failure of metabolic adaptation
Maternal drugs (β blockers and β agonists)
Prenatal/perinatal hypoxia-ischemia
Poor energy reserves
Prematurity (<37 weeks)
Intrauterine growth restriction
Birth weight <10th percentile (small-for-gestation)
Increased energy demand
Cold stress
Seizures
Sepsis
Heart failure
Endocrine causes
Transient and persistent hyperinsulinism (birth weight >90th percentile, maternal diabetes, maternal obesity)
Hypopituitarism
Congenital adrenal hyperplasia
Inborn errors of metabolism
Disorders of amino acid metabolism (e.g., maple syrup urine disease)
Disorders of carbohydrate metabolism (e.g., galactosemia, glycogen storage disease)
Disorders of fatty acid oxidation (e.g., CPT-1 deficiency, medium- and very long-chain acyl-CoA dehydrogenase deficiency)

Inadequate time for metabolic transition and fewer opportunities for skin-to-skin care and early feeding are likely responsible for hypoglycemia in infants delivered by cesarean section.[6]

Brain Injury in Neonatal Hypoglycemia

Animal Data

Animal models demonstrate that the newborn brain is resistant to injury than the mature brain during acute hypoglycemia, likely because of its ability to maintain energy metabolism using alternative substrates.[7–9] Scattered neuronal injury is seen in brain regions important for attention, learning, and emotion (anterior cingulate and orbital cortex) and cognitive function (temporal cortex).[7] Newborn nonhuman primates exposed to prolonged acute hypoglycemia (10 hours) have impaired motivation and adaptability in infancy and require additional training and procedural modification for learning the task.[10] Recurrent hypoglycemia in the neonatal period negatively impacts neurodevelopment, leading to increased anxiety, affective dysregulation, poor socialization, and altered stress response.[11,12] Animal studies also show that excess dextrose administration during treatment of hypoglycemia worsens brain injury.[9]

Human Data

Since first reported in 1959, over 60 studies have reported neurodevelopmental outcome after neonatal hypoglycemia. A review of 16 studies (89 infants) reported that more than 95% of infants with neurological sequelae had a plasma glucose <25 mg/dL (<1.4 mmol/L).[13] Most of the studies included in the review were retrospective, of small sample size, lacked a control group, or did not controlled for comorbidities. Boluyt and colleagues in a 2006 systematic review identified 18 eligible studies on neurodevelopmental outcome after neonatal hypoglycemia.[14] Only two were found to be of high methodologic quality. None of the studies provided a valid estimate of the effect of neonatal hypoglycemia on neurodevelopment. Since then, six studies of large sample size have been published (Table 2). They are briefly reviewed below:

In a cohort of 832 preterm infants of 32–35 weeks gestation, neurodevelopment was assessed at 43–49 months using ages and stage questionnaire (ASQ).[15] Children who had hypoglycemia (defined as blood glucose <30 mg/dL [<1.7 mmol/L]) in the first 72 hours after birth (*N*=67) had >2 folds higher odds of developmental delay (20% vs 9%), compared with those who did not have neonatal hypoglycemia (*N*=765).[15] Odds for abnormal ASQ total-problem scores increased with decreasing glucose levels with the glucose value <20 mg/dL (1.1 mmol/L) being associated with an odds ratio of 3.04 (95% CI: 1.03–9.00).[15] Glucose monitoring was not standardized in the study, which could have led to a selection bias. Treatment details were also not provided.

In a population-based study of approximately 2000 infants born at 23–42 weeks gestation, 1395 infants who had at least one recorded glucose measurement in the first three hours after birth were matched with their academic performance at 10 years.[3] Transient hypoglycemia (defined as a single blood glucose value below threshold) was associated with decreased probability of proficiency on literacy (adjusted odds ratio [ORs], 0.49, 0.43, and 0.62) and mathematics achievement tests (adjusted ORs, 0.49, 0.51, and 0.78) for the three hypoglycemia cutoffs (glucose level <35 mg/dL [<2.0 mmol/L], <40 mg/dL [<2.2 mmol/L], and <45 mg/dL [<2.5 mmol/L]), respectively.[3] These data are consistent with the learning difficulties demonstrated in nonhuman primates with prolonged neonatal hypoglycemia.[10] A limitation of the study is that glucose concentrations were determined only for the first two values in the first three hours of birth; the potential effects of persistent or late-onset hypoglycemia were not tested. Moreover, effects of treatment were not examined.[3]

A secondary analysis of data from a national, multisite, randomized controlled longitudinal intervention study of long-term health and developmental outcomes in preterm infants ≤37 week gestation and ≤2500 g birth weight did not find differences in cognitive, academic, and behavioral outcomes at 3, 8, or 18 years between infants who had neonatal hypoglycemia (blood glucose ≤45 mg/dL [≤2.5 mmol/L]; *N*=461) and those that remained normoglycemic (*N*=284) after adjusting for demographics and confounding variables.[5] Interestingly, children with a history of severe neonatal hypoglycemia (blood glucose ≤35 mg/dL [≤2.0 mmol/L]) had lower problematic behaviors than the other groups.[5] This study has limitations. In addition to being a secondary analysis, screening and treatment criteria were not standardized. Methods of glucose measurement were not uniform, and duration of hypoglycemia was not reported.

In a prospective study involving 614 at-risk infants, blood glucose concentration was determined up to one week after birth (more intensely in the first 48 hours).[16] Additionally, CGM was performed in a subset. Hypoglycemia, defined as blood glucose <47 mg/dL (<2.6 mmol/L) was treated using a combination of feeding, buccal dextrose gel application, or intravenous dextrose. Neurosensory impairment (NSI) and processing difficulty were evaluated in 404 infants at 2 years of age using bayley scales of Infant Development III, vision screening, global motion perception and executive function. The risk of NSI or processing difficulty was

Table 2: Recent studies on neurodevelopmental outcome after neonatal hypoglycemia

First author (year)	*Study type*	*Population and sample size*	*Hypoglycemia definition*	*Glucose monitoring and method*	*Treatment and goal*	*Age at follow-up*	*Neuro-developmental tests/outcomes*	*Main study results*
Kerstjens (2012)[15]	Retrospective cohort	32–35 weeks preterm infants. HG, 67; no-HG, 765	Plasma Glc, <30 mg/dL in first 72 hr	Several times during the first 24 hr and longer as necessary. Method not described.	Not mentioned	43–49 months	Ages and stages questionnaire/ developmental delay	>2 folds higher odds of developmental delay in those with HG. Higher odds with lower glucose values
Kaiser (2015)[3]	Retrospective cohort	All infants between 23 and 42 wk. HG, 89; no-HG, 1306	Glc <35 mg/dL (primary). <40 mg/dL and <45 mg/dL (secondary)	1–3 hr after birth, repeated in 1 hr in those with HG. Method not described.	No standardized treatment. IV dextrose or early feeding when glucose ≤35 mg/dL	10 years	Benchmark examination in fourth grade/ Proficiency on literacy and mathematics achievement tests.	Decreased probability of proficiency on literacy tests (adjusted ORs, 0.49, 0.43, and 0.62) and on mathematics tests (adjusted ORs, 0.49, 0.51, and 0.78) with glucose <35 mg/dL, <40 mg/dL, and <45 mg/dL
McKinlay (2015)[16]	Prospective cohort	Preterm and term at-risk infants. HG, 216; no-HG, 188	Glc <47 mg/dL	Regular measurement for 24–48 hours or until no concerns. Masked CGM in a subset.	Feeding, dextrose gel, and IV dextrose to maintain blood glucose at least 47 mg/dL	2 years	BSID-III, vision screening, global motion perception and executive function	No increase in NSI or processing with HG. Unstable glycemia and steep rise in blood glucose in those with NSI
Goode (2016)[5]	Retrospective cohort	≤37 weeks gestation and ≤2500 g birth weight. HG, 461; no-HG, 284	Glc ≤45 mg/dL	No standardized protocol. Highest and lowest Glc levels by Dextrostix and/or plasma sample.	No standardized treatment	3, 8, and 18 years	Cognitive, academic, and behavioral assessments*	No difference in cognitive, academic, and behavioral outcomes. Lower problematic behaviors in those with severe HG.
McKinlay et al. (2017)[17]	Prospective cohort	Preterm and term at-risk infants. HG, 280; no-HG, 197	Glc <47 mg/dL	Blood Glc and masked CGM up to 7 days	Treated to maintain blood glucose at least 47 mg/dL	4.5 years	BSID-III, vision screening, global motion perception, and executive function	No increase in neurosensory impairment with HG. Low executive function and visual motor dysfunction with HG. Highest risk with severe, recurrent or clinical undetected HG. Steeper rise in interstitial Glc in those who developed NSI between 2 and 4.5 years

(Contd...)

Table 2: (*Contd...*)

First author (year)	*Study type*	*Population and sample size*	*Hypoglycemia definition*	*Glucose monitoring and method*	*Treatment and goal*	*Age at follow-up*	*Neuro-developmental tests/outcomes*	*Main study results*
van Kempen (2020)[18]	Prospective, randomized, controlled trial	Late preterm (35–37 wk) and at-risk term infants. Lower-threshold group, 348; traditional-threshold group, 341	Plasma Glc <47 mg/dL between 3 and 24 hr	Before feeding at 3, 6, 9, 12, 18, and 24 hr after birth	Randomized 1:1 to lower-threshold (Glc <36 mg/dL) and traditional-threshold (Glc <47 mg/dL) groups. Goal: ≥36 mg/dL in lower threshold and ≥47 mg/dL in traditional-threshold group	18 months	BSID-III-NL	No differences in Bayley-III-NL scores in the two groups. More and severe HG in the low-threshold group; more diagnostic and treatment interventions in the traditional-threshold group

*Cognitive: stanford-binet intelligence scales, peabody picture vocabulary test-revised (PPVT-R) and PPVT-III, wechsler intelligence scale for children and wechsler abbreviated scale of intelligence; academic achievement: woodcock-johnson tests of achievement-revised; Behavior: Child Behavior checklist and the youth report behavior surveillance system: *BSID-III*, bayley scales of Infant and toddler development, third edition; *BSID-III-NL*, bayley scales of infant and toddler development, third edition, dutch version; *CGM*, continuous glucose monitoring; *Glc*, glucose; *HG*, hypoglycemia; *NSI*,neurosensory impairment

not higher in children with neonatal hypoglycemia, irrespective of its frequency and severity. On the contrary, there was an indication for NSI with higher and unstable glucose concentrations in the first 48 hours after birth. Children with NSI had slightly higher (approximately 3 mg/dL) interstitial glucose concentrations than those with normal neurosensory function. Greater time outside of a blood glucose range 54 mg/dL (3 mmol/L) to 72 mg/dL (4 mmol/L) was associated with a 40% higher risk of NSI, particularly, cognitive delay. A steeper rise in interstitial glucose following treatment of first hypoglycemia episode increased the risk of NSI.[16]

Four hundred seventy-seven of the 604 eligible children were followed at 4.5 years.[17] Cognitive, executive, visual, and motor functions were assessed. Similar to the assessment at 2 years, neonatal hypoglycemia was not associated with an increased risk of NSI at 4.5 years. However, the risk of impaired executive and visual motor functions was increased, especially in children with severe (blood glucose <35 mg/dL [<2.0 mmol/L]), recurrent (>1 episode), or hidden (detected only on CGM) hypoglycemia in the neonatal period. Unlike the effect at 2 years, there was no association between NSI and time outside the central blood glucose (54–72 mg/dL [4.0–5.0 mmol/L]) range. However, children who developed NSI between 2 and 4.5 years had a steeper rise in interstitial glucose concentration after hypoglycemia.[17] Collectively, these data suggest that (1) severe and recurrent hypoglycemia in the neonatal period is associated with neurosensory, visual motor, and executive function impairments in early childhood; (2) these deficits may not be apparent in early infancy; and (3) glycemic fluctuations may worsen neurological outcomes. A limitation of the study is that the cohort included only newborn infants at risk for hypoglycemia. Infants with these conditions are known to be at risk for abnormal neurodevelopment even in the absence of hypoglycemia. Relevance of the data to healthy newborn infants with transient hypoglycemia is not known.

A recent multicenter trial (Hypoglycemia–Expectant Monitoring vs Intensive Treatment trial; the HypoEXIT trial) randomized late preterm and full-term infants at risk for hypoglycemia to treatment at a blood glucose <36 mg/dL (<2 mmol/L; lower-threshold group; *N*=348) or <47 mg/dL (<2.6 mmol/L; traditional-threshold group; *N*=341). The goal was to maintain blood glucose ≥36 mg/dL in the lower threshold group, and ≥47 mg/dL in the traditional-threshold group.[18] Neurodevelopment was assessed at 18 months of age. Cognitive and motor outcome scores were similar in the two groups. Infants in the lower-threshold group had more frequent and severe hypoglycemia than the traditional-threshold group. Conversely, there were more invasive diagnostic and treatment interventions in the traditional-threshold group.[18] The results cannot be extrapolated to all infants as the trial excluded neonates with severe hypoglycemia. Further, as mentioned above,[16,17] impairments may not become apparent until later in childhood. Long-term follow-up is necessary before treatment at lower glucose threshold can be recommended.

A meta-analysis involving 11 studies and 1657 infants demonstrated no association between neonatal hypoglycemia and NSI, risk of epilepsy, cognitive impairment, emotional and behavioral difficulty, visual and hearing impairment, motor deficits, and cerebral palsy in early childhood (2–5 years).[19] However, children with a history of neonatal hypoglycemia had a 3.5-fold higher risk of visual–motor impairment and a 2.5-fold higher risk of executive dysfunction. There was a statistically nonsignificant association between hypoglycemia and low language and literacy.

Assessment at mid-childhood (6–11 years) showed that neonatal hypoglycemia increased the risk of NSI by 3.6 folds and the risk of low language/literacy and numeracy by 2 folds. A statistically nonsignificant risk of emotional–behavioral difficulty was present. There was no impact on risk of epilepsy, motor, cognitive, visual, and hearing impairments.[19]

There are no outcome data at adolescence and beyond.

Management Considerations

The primary goal of screening and treatment of neonatal hypoglycemia is prevention of brain injury. Current diagnosis and treatment strategy is based on blood glucose levels and is focused on raising blood glucose concentrations above a predetermined threshold. While practical, this strategy may not ensure neuroprotection for the following reasons: (1) blood glucose levels do not reflect the dynamic metabolic changes in the developing brain during hypoglycemia;[8] (2) the risk of brain injury cannot be predicted by a single blood glucose without considering the severity and duration of hypoglycemia, availability of alternative substrates and associated comorbidities; and (3) there is no evidence that normalizing blood glucose above a certain level (typically, >45 mg/dL, >2.5 mmol/L) ensures neuroprotection.[3,20,21] Nevertheless, in the absence of an alternative evidence-based strategy, a blood glucose-based management strategy remains the recommendation of professional societies (Table 3).[22–26]

Screening

Universal screening will pick-up all cases of hypoglycemia. The disadvantages of this strategy are pain associated with blood collection, parental anxiety, over diagnosis and unnecessary treatment of a transient and potentially benign condition, and increased healthcare cost. Up to 39% of healthy full-term infants have at least one blood glucose concentration <47 mg/dL in the first five days after birth.[2] Currently, all professional societies recommend screening only infants at-risk for hypoglycemia.[22–26] This strategy is cost-effective but could miss asymptomatic hypoglycemia in infants without known risk factors. The concerns on unnecessary intervention remain and it is not clear whether such a screening and treatment strategy ensures normal neurodevelopment for the reasons mentioned above.[3,20,21]

Typical recommendation is to screen at-risk infants for hypoglycemia within 1–4 hours of birth, typically 30–60 minutes after a feeding, and then every 3–4 hours until two to three consecutive pre-prandial blood glucose levels in the normal range are confirmed. The duration of monitoring depends on the underlying risk factor.[22,24] However, a uniform duration of screening may be appropriate and easier to implement as there is no difference in the incidence and severity of hypoglycemia among the various risk groups.[4] The fact that hypoglycemia could occur after several normal blood glucose values in up to one third of infants and that 6% have the first episode of hypoglycemia on the second day [4] also supports a uniform length (e.g., 48 hours) of screening.

Screening is commonly performed using point-of-care nonenzymatic methods. Although convenient, point-of-care techniques are not sensitive at lower glucose levels and require confirmation using an enzymatic method in the laboratory. Hand-held point-of-care enzymatic methods are available. While they are more expensive per test, they are overall cost-effective because of the reduced need for laboratory confirmation.[27] Continuous monitoring of interstitial glucose using indwelling catheters is an alternative method. The method is reliable, detects "hidden" hypoglycemia[16,17] and reduces the need for intermittent glucose monitoring, but may result in over diagnosis and treatment.

Treatment

The primary goal of treatment is prevention of brain injury. Treatment depends on blood glucose concentration, presence or absence of symptoms and signs, infant's ability to feed, and response to intervention. Symptomatic infants, particularly those exhibiting neurological signs, require prompt measures to raise their blood glucose. Typically, an intravenous bolus of 10% dextrose at a dose of 200 mg/dL (2 ml/kg), followed by a continuous dextrose infusion at a glucose infusion rate (GIR) of 5–8 mg/kg per minute is provided.[22,28] The goal is to achieve a blood glucose concentration 40–50 mg/dL (2.2–2.8 mmol/L).[22] Some professional societies recommend a target range of 47–80 mg/dL (2.6–5.0 mmol/L) for infants <72 hours of age and 60–80 mg/dL (3.3–5.0 mmol/L) for those 72 hours or older.[24] The Pediatric Endocrine Society recommends maintaining plasma glucose >50 mg/dL (>2.8 mmol/L) during the first 48 hours, and >60 mg/dL (>3.3 mmol/L) after 48 hours in high-risk infants without suspected congenital hyperinsulinism.[23] A higher target (>70 mg/dL) is recommended for those with suspected or confirmed hyperinsulinism.[23] The target glucose concentration is maintained by frequent blood glucose checks and adjustment to infusion rate. IV dextrose is weaned when blood glucose remains stable for 12 hours.[24] Persistent hypoglycemia, requirement of high GIR (≥8 mg/kg per min), or inability to wean dextrose infusion after 3 days indicates the possibility of hyperinsulinism and the need for additional work-up.[24,26]

Asymptomatic infants who are able to feed are offered breastfeeding or formula with follow-up blood glucose checks 1 hour later.[22,24] Some professional societies use different blood glucose thresholds depending on postnatal age (e.g., <25 mg/dL [<1.4 mmol/L] in the first 4 hours and <35 mg/dL [<1.9 mmol/L]

Table 3: Operational thresholds for management of neonatal hypoglycemia

	Postnatal age (hours)				
Professional Society	*0–4*	*4–24*	*24–48*	*48–72*	*>72*
American Academy of Pediatrics[22,a]	<25	<35	–	–	–
Pediatric Endocrine Society[23,b]	Maintain plasma glucose >50			Maintain Glc. >60	
World Health Organization[35]			<47		
Canadian Pediatric Society[24]			<47		<60
British Association of Perinatal Medicine[26]	<18 any time; a single value <40 in a symptomatic infant; two values <36 in asymptomatic at-risk infant				

Values are mg/dL; to get mmol/L, multiply by 0.0555. *Glc*, glucose: [a]Symptomatic infants with blood glucose <40 mg/dL require IV glucose: [b]Maintain plasma glucose >70 mg/dL in suspected/confirmed congenital hyperinsulinism

between 4 and 24 hours).[22] One study showed that formula feeding led to higher blood glucose than breastfeeding or feeding of expressed breastmilk.[29] Intravenous dextrose with or without a mini bolus as described above is used if blood glucose remains low. Approximately 5% of infants with hypoglycemia require parenteral dextrose.[6]

Dextrose Gel for Prevention and Treatment of Hypoglycemia

Application of 40% dextrose gel to the buccal mucosa at a dose of 0.5 mL/kg (200 mg/kg) has emerged as an alternative to intravenous dextrose infusion.[24,29–31] Dextrose gel application is followed with breastfeeding or bottle feeding of expressed mother's milk, donor breastmilk, or formula. Type of feeding determines success with dextrose gel. In one study, donor milk and formula achieved higher blood glucose levels than breastfeeding.[32] The primary benefit of dextrose gel is improved success with breastfeeding, likely because of the mother and infant can remain together.[30,31] There was no effect on NSI at 2 years of age.[20,33] Preventive application of dextrose gel reduces the risk of hypoglycemia in at-risk infants.[34]

Conclusions

Despite being a common metabolic problem with the potential to cause brain injury, diagnosis and management of neonatal hypoglycemia remains controversial. Severe and recurrent hypoglycemia is associated with impaired executive and visual motor functions in infants at high-risk for hypoglycemia. Detection of these impairments at preschool age suggests the need for long-term follow-up in children exposed to neonatal hypoglycemia. The higher risk of NSI with glycemic instability suggests the importance of avoiding glycemic fluctuations during treatment. Current recommendations from professional societies are expert opinions and not evidence based. Well-designed, prospective, randomized, controlled trials with long-term neurodevelopmental assessment are needed to optimize management.

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