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Neonatal hypoglycaemia

Jane E Harding [1], Jane M Alsweiler,[2,3] Taygen E Edwards,[1] Chris JD McKinlay[2,4]

For numbered affiliations see end of article.
Correspondence to: Professor Jane E Harding, Liggins Institute, University of Auckland, Auckland 1142, New Zealand; j.harding@auckland.ac.nz

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ABSTRACT

Low blood concentrations of glucose (hypoglycaemia) soon after birth are common because of the delayed metabolic transition from maternal to endogenous neonatal sources of glucose. Because glucose is the main energy source for the brain, severe hypoglycaemia can cause neuroglycopenia (inadequate supply of glucose to the brain) and, if severe, permanent brain injury. Routine screening of infants at risk and treatment when hypoglycaemia is detected are therefore widely recommended. Robust evidence to support most aspects of management is lacking, however, including the appropriate threshold for diagnosis and optimal monitoring. Treatment is usually initially more feeding, with buccal dextrose gel, followed by intravenous dextrose. In infants at risk, developmental outcomes after mild hypoglycaemia seem to be worse than in those who do not develop hypoglycaemia, but the reasons for these observations are uncertain. Here, the current understanding of the pathophysiology of neonatal hypoglycaemia and recent evidence regarding its diagnosis, management, and outcomes are reviewed. Recommendations are made for further research priorities.

Introduction

Neonatal hypoglycaemia (low blood concentrations of glucose) is the most common metabolic abnormality of the newborn, with glucose concentrations <2.6 mmol/L found in about 40% of neonates.[1] Neonatal hypoglycaemia occurs mainly in the first hours and days after birth as the neonate makes the transition from a continuous intravenous glucose supply across the umbilical circulation to the intermittent feed and fast cycle of milk feeding. Severe hypoglycaemia can cause brain injury and can be life threatening.[2 3] The consequences of mild hypoglycaemia are less certain, however, and the definitions of both vary widely.[4] Also, mild hypoglycaemia is commonly asymptomatic, so screening by intermittent blood testing is usually recommended for infants at increased risk, with treatment when low levels of glucose are detected.[5 6] Up to 30% of infants belong to commonly accepted risk categories,[5] making the risk of neonatal hypoglycaemia arguably the most common reason for medical intervention in neonates after initial resuscitation.

Although the pathophysiology of this common problem is beginning to be understood, high certainty evidence on which to base clinical decisions is scarce. This lack of evidence contributes to the wide variation in practice of screening protocols, thresholds for diagnosis, and appropriate treatment. Over the past ten years, several randomised trials and large cohort studies have provided new insights into these and other aspects of neonatal hypoglycaemia. Some promising new approaches that could enhance the management of neonatal hypoglycaemia in the future have also been reported. Here, we review the more recent evidence on the management of neonatal hypoglycaemia, with a focus on transitional neonatal hypoglycaemia, areas of continuing uncertainty, and potential future developments.

Sources and selection criteria

Between March and April 2023, we searched PubMed and Medline for articles on neonatal hypoglycaemia published between 1 January 2010 and 31 March 2023. We cross referenced the search terms "hypoglycaemia," "hypoglycemia," "glucose," "glycaemia", "glycemia," "dextrose gel," "glucagon," and "diazoxide," with variations of neonate, including "neonate," "postnatal," "baby," and "infant." We selected more recent publications but did not exclude commonly referenced and highly regarded older publications. We searched only for articles published in English, or those translated into English. We also searched reference lists of articles identified by this strategy and selected those we judged to be relevant. We prioritised peer reviewed systematic reviews and large clinical trials, but also included observational studies, retrospective studies, guidelines, and review articles.

Definitions

Hypoglycaemia, defined as low blood concentrations of glucose, is not in itself a diagnosis, but rather a screening test for an inadequate brain supply of glucose (neuroglycopenia) and, rarely, a sign of an underlying endocrine or metabolic disorder. Neonatal hypoglycaemia can be classified by the type of episodes, cause, and time course, although overlap can occur with respect to the underlying pathophysiology, and distinction between the different groups is often only possible in retrospect.[7] An episode refers to one or more sequential blood glucose concentrations below a defined operational threshold. Episodes are further classified by the lowest concentration of glucose, with a severe episode commonly defined as <2.0 mmol/L and a mild episode ≥2.0 mmol/L, and by their frequency, with recurrent hypoglycaemia commonly defined as three or more episodes (table 1).

Table 1 | Commonly used definitions in hypoglycaemia. Definitions of thresholds such as mild and severe vary widely

Term	Definition
Hypoglycaemic episode	One or more measurements of glucose concentration below a defined operational threshold
Severe episode	Lowest glucose concentration <2.0 mmol/L
Mild episode	Lowest glucose concentration <2.6 mmol/L
Recurrent hypoglycaemia	≥3 episodes
Transitional hypoglycaemia	Low concentrations of glucose caused by delayed metabolic transition after birth
Prolonged transitional hypoglycaemia	Transitional hypoglycaemia persisting beyond 72 hours after birth
Operational threshold	Glucose concentration when intervention is considered appropriate to minimise risk of brain injury
Neuroglycopenia	Inadequate brain metabolic substrates for glycolysis

Classification of neonatal hypoglycaemia

In term and near term newborn infants who do not have any underlying disorders and are otherwise healthy, hypoglycaemia is classified as transitional, representing a delay in the normal physiological adaptation from fetal life. About 40% of infants with transitional hypoglycaemia have severe or recurrent episodes.[8] Secondary causes of hypoglycaemia include acute illness, such as sepsis and hypoxic ischaemic encephalopathy, and moderate or very preterm birth. The primary causes include congenital malformations that affect endocrine function, and genetic disorders of glucose or intermediary metabolism. Transitional neonatal hypoglycaemia often resolves within 48 hours and is considered brief, but occasionally transitional neonatal hypoglycaemia persists beyond 72 hours and is termed prolonged transitional hypoglycaemia. Prolonged transitional hypoglycaemia usually resolves within weeks but can continue for a few months and is a diagnosis of exclusion, made in retrospect.[9]

Primary causes should be considered, particularly in the presence of acidosis or alkalosis; bradycardia or arrhythmia; conjugated hyperbilirubinaemia; micropenis, microcephaly, or cleft palate (potential markers of hypothalamic or pituitary defects); a family history of infant hypoglycaemia; persistently absent ketones; very high insulin concentrations; or a normal insulin:glucose ratio during hypoglycaemia (≤1.0 mU/mmol). The rate of prolonged transitional hypoglycaemia is reported to be about six per 10 000 births.[10] The primary inherited causes are similarly rare, usually requiring ongoing treatment and monitoring throughout infancy, and are sometimes referred to as persistent hypoglycaemia of infancy.

Physiology of the metabolic transition

The physiological changes that support transition from fetal to extrauterine life are profound, unique, and unequalled elsewhere in the life course. Survival after birth depends on establishing pulmonary blood flow, lung aeration, and regular breathing.[11] After this initial cardiopulmonary transition, ongoing survival depends on activation of the liver to provide energy substrates, previously supplied by the placenta, to support oxidative metabolism of tissues. Adequate hepatic energy production is crucial, especially until enteral feeds are well established. In the early newborn period, glucose is the main energy substrate, followed by lactate and ketone bodies,[12] although ketogenesis in the first 6-12 hours after birth is minimal, even in healthy neonates.[13 14]

With normal uteroplacental function, the fetus receives a continuous supply of glucose from the mother, and fetal glucose synthesis is negligible. This process allows the fetus to maintain an anabolic state to achieve growth, and a high fetal insulin to glucagon molar ratio (up to 10-15) promotes glycogenesis and lipogenesis in preparation for postnatal life.[15 16] With the cutting of the cord, infants must start hepatic glucose output from glycogenolysis and gluconeogenesis to prevent hypoglycaemia and neuroglycopenia. In late gestation, mean fetal glucose concentrations are about 3.5 mmol/L[17 18] and increase to about 4.6 mmol/L during normal labour. Slightly higher concentrations are reported after instrumental birth (about 5.8 mmol/L) and lower concentrations after elective caesarean section (about 3.9 mmol/L).[19–21] After birth, neonatal blood glucose concentrations fall to a mean of about 2.9 mmol/L by age 30 minutes,[22 23] increasing to about 3.1 mmol/L by age 60-90 minutes.[24 25] Thereafter, mean blood glucose concentrations before feeding in healthy, breastfed, term infants are 3.3 mmol/L in the first 48 hours after birth, gradually increasing to 4.5 mmol/L by 96 hours.[1 14 26] The 10th centile for blood glucose concentrations in the period from two to 48 hours after birth in healthy, term, breastfed infants is 2.6 mmol/L (figure 1).[1 14]

Before birth, the rise in fetal cortisol production in late pregnancy induces expression of several hepatic enzymes that represent rate limiting steps in glucose production, including phospho-phenolpyruvate carboxykinase (gluconeogenesis) and glucose-6-phosphatase (glycogenolysis and gluconeogenesis).[27 28] In rodents and sheep, the main trigger for the onset of hepatic glucose production after birth is a rapid fall in the insulin to glucagon ratio, mainly because of a surge in glucagon secretion from pancreatic α cells but also from reduced release

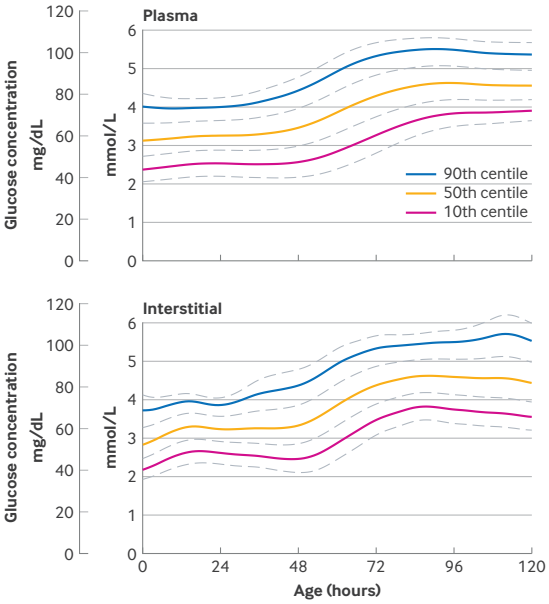

Figure 1 | Centiles of plasma and interstitial concentrations of glucose over the first five days in healthy term newborns. The 10th centile, in the period from two to 48 hours after birth, is about 2.6 mmol/L. Adapted and reproduced with permission from Harris et al[1]

of insulin from β cells.[16 29] Similar physiology has been shown in the human neonate.[30] The mechanisms that underlie the postnatal adaptations in the endocrine pancreas are not fully understood, although the peripartum surges in fetal catecholamines, thyroxine, and cortisol are likely to play a part (figure 2).[29] An important functional change in the β cell that supports postnatal glucose homeostasis is an increasing ability to suppress secretion of insulin at low concentrations of blood glucose, which requires an increase in the low fetal glucose set point for secretion of insulin.[30 31] Recent evidence in rodents suggests that the shift of β cells from constitutive to mature glucose regulated insulin secretion after birth might be mediated by activation of dynamic signalling from the mechanistic target of rapamycin complex 1 (mTOR1).[32]

With the fall in the insulin to glucagon ratio, lipolysis increases and glycerol is produced, providing a key substrate for gluconeogenesis as glycogen is depleted.[33 34] Thyroxine and cortisol also enhance lipolysis in neonates.[35 36] As hepatic fatty acid oxidation increases on the first day, more cofactors and ATP are generated within the liver to support gluconeogenesis, whereas fatty oxidation in peripheral tissues inhibits glucose oxidation and stimulates the production of more gluconeogenic precursors, including lactate, pyruvate, and alanine.[37]

Pathophysiology of neonatal hypoglycaemia

Although some infants with transitional hypoglycaemia can have high concentrations of insulin, the most common physiological feature of these infants is inadequate suppression of insulin at low concentrations of blood glucose, indicating a delay

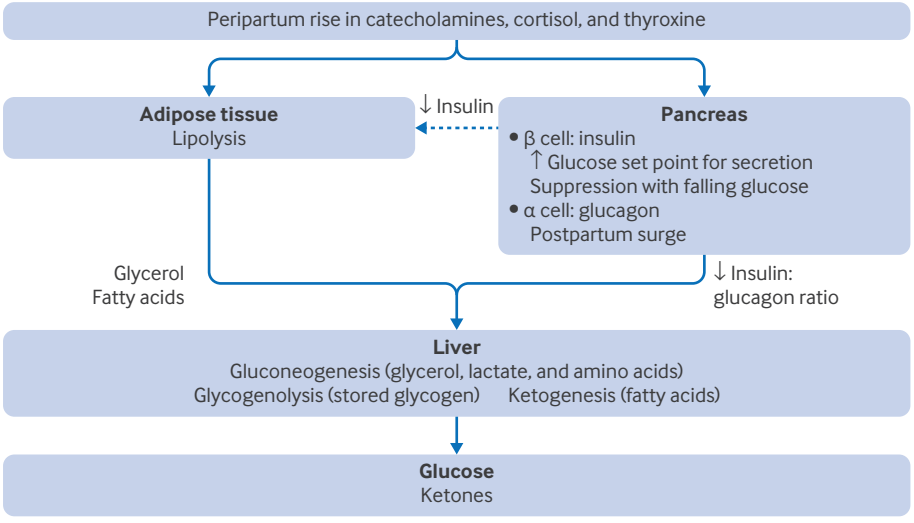

Figure 2 | Postnatal adaptations to support glucose homeostasis. Catecholamines, cortisol, and thyroxine stimulate lipolysis in adipose tissue and glucagon secretion from pancreatic α cells. Pancreatic β cells transition from constitutive to mature glucose regulated insulin secretion, which involves a rise in the glucose set point for release of insulin and greater suppression of insulin as blood concentrations of glucose fall. The decreasing insulin to glucagon ratio after birth is a key stimulus for hepatic glucose output, triggering both glycogenolysis (release of glucose from stored glycogen) and synthesis of glucose (gluconeogenesis) from glycerol (product of lipolysis), lactate, and other precursors, including gluconeogenic amino acids (eg, alanine). Increasing hepatic fatty acid oxidation on the first day not only provides substrate for ketogenesis but also generates more cofactors and ATP in the liver to support gluconeogenesis. Increasing fatty oxidation in peripheral tissues produces more gluconeogenic precursors

in postnatal adaptation of the β cell from the fetal state.[10] Thus insulin concentrations in infants with transitional hypoglycaemia are typically not high but are inappropriately raised for the preprandial state.[10]

The physiological mechanisms underlying impairments in metabolic transition are not fully understood. In sheep, fetal growth restriction results in chronically raised concentrations of catecholamines that suppress fetal secretion of insulin; loss of this negative feedback after birth seems to contribute to persistence of a more fetal-like pattern of insulin secretion.[38] Studies in rodents suggest that the blood glucose threshold for insulin secretion in the immature β cell is inversely proportional to the cell surface density of ATP sensitive potassium channels (K_{ATP}).[39] K_{ATP} contribute to cell membrane polarisation by potassium efflux and are responsible for depolarisation as glucose generated ATP increases (channel closure reduces potassium ion efflux), triggering release of insulin vesicles. Hypoxia seems to reduce K_{ATP} density, resulting in decreased membrane polarity and a lower threshold for release of insulin, although the effect of clinical risk factors on K_{ATP} trafficking has yet to be determined. Similarly, relatively little is known of the effect of pregnancy complications on α cell development,[40] but maternal glucose intolerance could result in β cell hyperplasia or hypertrophy, or both,[41] and decrease fetal α cell proliferation in late pregnancy.[42] The peptide hormone urocortin 3 could have a role in fine tuning both β cell and α cell maturation.[43]

The main metabolic consequence of a failure to adequately suppress secretion of insulin after birth as blood concentrations of glucose fall is reduced hepatic glucose output and impaired ketogenesis.[10 30] This mechanism contributes not only to the risk of neuroglycopenia but also to the lower than average blood concentrations of glucose seen in infants with transitional hypoglycaemia. Insulin inhibits lipolysis in adults, but release of glycerol and fatty acids might be relatively preserved in newborn infants,[44 45] possibly a result of a greater counter-regulatory effect of cortisol and catecholamines in adipose tissue than in the liver.[46] Thus even infants with severe hypoglycaemia usually have detectable free fatty acids in plasma, although ketones are frequently absent.[10]

Neuropathology of hypoglycaemic injury

The neonatal brain is dependent on a continuous supply of glucose to generate energy as ATP, because developing neurons have reduced capacity to use alternative substrates and limited high energy phosphate reserves.[47] Also, rodent studies have shown that maximal expression of glucose transporter proteins (GLUT1 and GLUT3) at the blood-brain barrier that enable glucose uptake into the brain by facilitated diffusion might take several days to weeks.[47]

Neuroglycopenia describes a state of metabolic imbalance caused by low glycolysis that triggers a series of cellular events that impair function, cause injury and, if not reversed, ultimately lead to cell necrosis. Rodent studies have indicated that at least three mechanisms could contribute to cytotoxicity in neuroglycopenia (figure 3).[48 49] Firstly, neuronal depletion of pyruvate, which is normally oxidised by the citric acid cycle, results in intracellular deficiency of oxaloacetate. This deficiency in turn leads to excess generation of the excitatory neurotransmitter glutamate, which is released into the extracellular space around neurons and causes sustained influx of calcium by means of the glutamate receptor, thereby initiating excitotoxicity. High intracellular concentrations of calcium activate several enzymes, including phospholipases, endonucleases, and proteases, which damage cell structures.

Secondly, an increase in free intracellular zinc, caused by excitatory release and influx of calcium and damage to zinc containing organelles, activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to superoxide production in mitochondria. Thirdly, hyperactivation of poly-ADP-ribose-polymerase 1 (PARP-1) by calcium and superoxide contributes to mitochondrial damage and cytosolic depletion of nicotinamide adenine dinucleotide (NAD+), which further inhibits glycolysis. Neuroglycopenia mainly affects neurons, although glial cells could be susceptible to injury when hypoglycaemia is combined with hypoxia.[50] Hypoglycaemia induced apoptosis has also been reported in immature oligodendrocytes.[51]

A key challenge in the management of neonatal hypoglycaemia is the current lack of clinical devices that can detect and monitor neuroglycopenia. Furthermore, as cell injury progresses, giving exogenous glucose could worsen cell injury. When NAD+ is depleted during hypoglycaemia, reperfused glucose is shunted through the hexose monophosphate pathway, generating NADPH and more superoxide.[52] Of concern is that in rodent studies, the rate of superoxide production is proportional to blood glucose concentrations after insulin induced hypoglycaemia.

This phenomenon of glucose reperfusion injury could explain why apparently brief, mild episodes of neonatal hypoglycaemia, if untreated, have been associated with reduced educational achievement,[53] althought in infants who have received treatment, identifying a safe lower limit and length of neonatal hypoglycaemia has proved challenging.[54] Glucose reperfusion injury also raises the question of the extent to which the long term cognitive deficits after severe or recurrent hypoglycaemia[8] are caused by hypoglycaemia itself or the interventions received. For example, in a large prospective cohort of 477 infants born at risk of transitional hypoglycaemia, those with neurosensory impairment at age two and 4.5 years had higher and more rapid increases

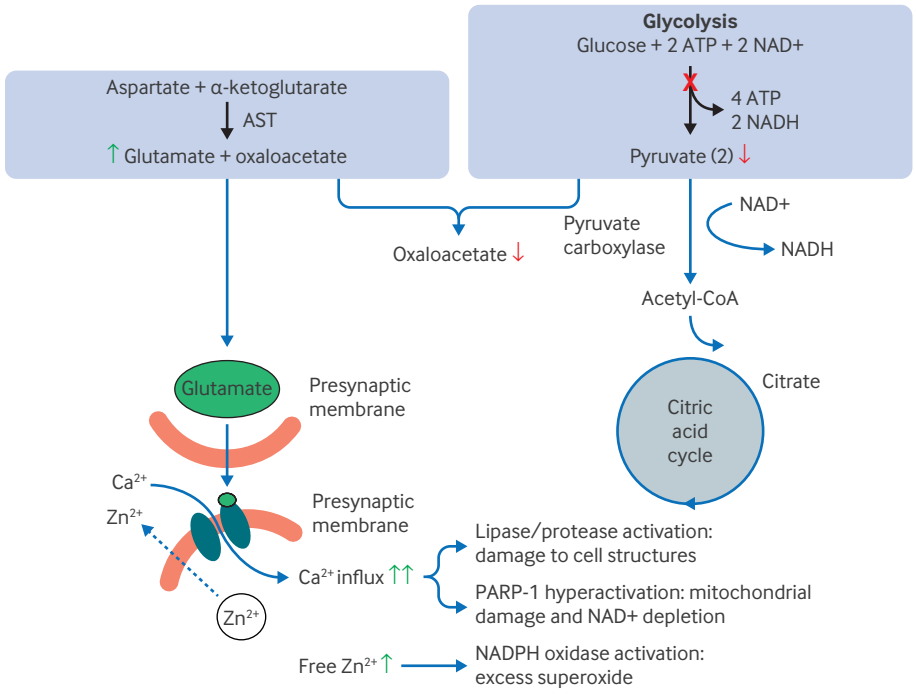

Figure 3 | Schematic model of cellular mechanisms in neuroglycopenia. Suppression of glycolysis from reduced neuronal uptake of glucose depletes intracelluar pyruvate, which in turn reduces production of oxaloacetate by the citric acid cycle and pyruvate carboxylase. Replenishment of oxaloacetate by aspartate transaminase (AST) generates excess glutamate, an excitatory neurotransmitter. Increasing amounts of glutamate in the extracellular fluid around neurons causes sustained neuronal excitation by glutamate receptors. High calcium (Ca^{2+}) influx initiates excitotoxicity, including hyeractivation of poly-ADP-ribose-polymerase 1 (PARP-1), contributing to mitochondrial damage and cytosolic depletion of nicotinamide adenine dinucleotide (NAD+). An increase in free zinc (Zn^{2+}) stimulates excess reactive oxygen species by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NADH=reduced nicotinamide adenine dinucleotide; acetyl-CoA=acetyl coenzyme A

in blood concentrations of glucose after hypoglycaemia, especially after treatment with exogenous dextrose.[55 56]

In several animal studies, treating hypoglycaemia with substrates that can be metabolised without NAD+, such as lactate, ketones, and pyruvate, reversed cell injury,[57–59] suggesting that these subtrates could have a neuroprotective role in neonatal hypoglycaemia. The extent to which this effect occurs in humans has yet to be studied.

Challenges in screening for hypoglycaemia

Neonatal hypoglycaemia is commonly asymptomatic, unless severe, and clinical assessment has poor sensitivity and specificity for detecting infants with low blood concentrations of glucose.[6] Therefore, most guidelines recommend that infants with known risk factors (eg, maternal diabetes, small or large for gestation, or born preterm) are screened by regular testing for blood glucose concentrations,[5] but there are several difficulties with this approach.

Firstly, screening for neonatal hypoglycaemia arguably does not meet the criteria for a valid screening programme (table 2).[60] Screening programmes should look for a condition where the natural history of the disease is understood, a reliable diagnostic test for the condition of interest in those with a positive screen (in this case, neuroglycopenia) is available, a treatment that has been shown to improve outcomes for those at a presymptomatic stage compared with usual care is available, and the overall benefits of screening should outweigh the harm.[61–63] The natural history of transitional neonatal hypoglycaemia and its effects on long term neurodevelopmental outcomes, however, are not well understood.[4 64] No direct evidence exists from randomised trials that treatment of hypoglycaemia improves long term neurodevelopmental outcomes[65] or that the benefits of screening outweigh harm. For some infants, screening might cause more harm than good. As well as the pain caused by heelprick blood tests,[66] in retrospective observational studies of 10 533 and 10 965 infants, respectively, those who were screened for neonatal hypoglycaemia were more likely to be given formula and less likely to be exclusively breastfed, even if their blood glucose concentrations were normal.[67 68] Infants with risk factors for neonatal hypoglycaemia, however, such as those whose mothers had diabetes and those born by caesarean section, had a higher risk of not being breastfed, independent of hypoglycaemia,[69] so determining if this association is causal is difficult.

Secondly, operational thresholds to define neonatal hypoglycaemia in asymptomatic infants

Table 2 | Assessment of screening for neonatal hypoglycaemia against the criteria for an effective screening programme

	Screening principle[50]	Comments	Meets criteria
Condition	The condition should be an important health problem	Severe neonatal hypoglycaemia is rare but probably causes brain injury. Transitional hypoglycaemia is common and associated with developmental delay	Yes
	The natural history of the condition, including development from latent to declared disease, should be adequately understood	The natural history of the condition (ie, the risk of brain injury from transitional neonatal hypoglycaemia) is poorly understood	No
	A recognisable latent or early symptomatic phase should be present	Hypoglycaemia is commonly asymptomatic. Even one incidence of a low blood glucose concentration, however, has been associated with poor academic outcomes	Maybe
Test	A suitable test or examination should be available	Testing for blood concentrations of glucose is simple, although painful. A reliable test for neuroglycopenia to determine which infants with a positive screening test would benefit from intervention is not yet available	No
	The test should be acceptable to the population	No data on acceptability of the test to parents or infants (as adults)	No
Intervention	An accepted treatment for patients with recognised disease should be available	Treatment options include oral dextrose gel, formula, intravenous dextrose, diazoxide, and glucagon. No direct evidence exists that any of these interventions improve neurodevelopment	No
	An agreed policy on who to treat as patients should exist	Target population varies from country to country, but all guidelines recommend screening infants born preterm, small for gestational age, and to mothers with diabetes. Screening in infants born large for gestational age is contentious	Yes
Screening programme	The cost of case finding (including diagnosis and treatment of patients with a diagnosis) should be economically balanced in relation to possible expenditure on medical care as a whole	No data are available on the cost effectiveness of screening for neonatal hypoglycaemia	No
Implementation criteria	Case finding should be a continuing process and not a once and for all project	—	Yes
	Facilities for diagnosis and treatment should be available	Inaccurate non-enzymatic analysers are frequently used to diagnose neonatal hypoglycaemia	Maybe

vary because of the uncertain relation between blood concentrations of glucose and neuroglycopenia, with different guidelines ranging from blood glucose thresholds of <2.0 mol/L[70] to <2.8 mmol/L[9] (table 3). In a large, randomised controlled trial, 689 infants with mild hypoglycaemia were randomised to a lower threshold (treatment given at a glucose concentration of <2.0 mmol/L) or a traditional threshold (treatment given at a glucose concentration of <2.6 mmol/L). The lower threshold was non-inferior to the traditional threshold for neurodevelopmental outcome at age 18 months.[71] Assessing neurodevelopment is more accurate when children are older, however, and age 18 months might be too young to detect important, higher cognitive functions that emerge at later stages of development, especially executive function and advanced visual-motor integration. Furthermore, screening is often done with inaccurate cotside tests,[72] although more accurate and likely cost saving methods are now available.[73]

Thirdly, although about 50% of 514 infants with traditional risk factors (infant of a mother with diabetes, large or small birth weight, and born preterm) developed hypoglycaemia, in a recent prospective observational study, the frequency of low blood concentrations of glucose was similar in 67 healthy term infants with no risk factors.[1 74] Also, in retrospective observational studies, either none of the risk factors used for screening were associated with hypoglycaemia[75] or only insulin treatment for maternal gestational diabetes was predictive.[76] Although the frequency of hypoglycaemia in infants with risk factors might not be greatly increased, these infants could be more sensitive to the effects of hypoglycaemia on neurodevelopment than infants

Table 3 | Examples of guidance for management of asymptomatic neonatal hypoglycaemia

Guideline (listed in date order); scope	Glucose concentration threshold for intervention (mmol/L)	Target glucose concentration during treatment (mmol/L)	First line treatment	Second line treatment	Third line treatment	Length of monitoring if glucose normal	Length of monitoring after last low glucose measurement	Further investigation and referral
WHO 1997[122]; newborns at risk	<2.6	>2.6	Feeding	Intravenous 10% dextrose 60 mL/kg/day	NS	NS	NS	NS
AAP 2011[78]; late preterm and term infants at risk	<1.4 if <4 hours, <1.9 if 4-24 hours	>2.5 before feeds	More feeding	Intravenous 10% dextrose 80-100 mL/kg/day (5-8 mg/kg/min) or bolus 2 mL/kg 10% dextrose, or both	NS	12 hours for infant of mother with diabetes and large for gestational age, 24 hours for preterm and small for gestational age	NS	Glucose <2.5 mmol/L after 24 hours, intravenous dextrose 5-8 mg/kg/min
BAPM 2017[106]; term newborns in first 48 hours	<1.0 or two values <2.0	≥2.0 initially, ≥2.6 if receiving intravenous dextrose	Feeding support	Buccal 40% dextrose gel 0.5 mL/kg with feeding support	Intravenous 10% dextrose 60 mL/kg/day	Until two glucose samples ≥2.0 mmol/L taken before feeds	Until glucose ≥2.6 mmol/L for at least 24 hours	>8 mg/kg/min intravenous dextrose
Canada 2019[107]; newborns at risk	<2.6 if <72 hours, <2.8 if ≥72 hours	>2.6 if <72 hours, >3.3 if ≥72 hours	More feeding	Buccal 40% dextrose gel 0.5 mL/kg with feed	Intravenous 10% dextrose 80 mL/kg/day (5.5 mg/kg/min). Bolus 2 mL/kg 10% dextrose	12 hours for infant of mother with diabetes and large for gestational age, 24 hours for small for gestational age and preterm	Until two samples in normal range taken before feeds	>10 mg/kg/min intravenous dextrose and aged >72 hours
Switzerland 2020[123]; late preterm and term infants on maternity wards	<2.6	≥2.6	Buccal 40% dextrose gel 0.5 mL/kg with more feeds	NS	NS	Three measures ≥2.6 mmol/L taken before feeds	NS	Glucose <2.6 mmol/L after feeds with dextrose gel
ABM[109]; late preterm and term infants	<2.5	≥2.5	More feeding	Buccal 40% dextrose gel 0.5 mL/kg with feeding plan	Intravenous dextrose bolus 1-2 mL/kg 10% dextrose, infusion 5-8 mg/kg/min	Three measures ≥2.5 mmol/L taken before feeds, preterm and small for gestational age for 24 hours	Blood glucose >3.9 mmol/L over several fast feed cycles if hypoglycaemia persists for >4 days or requiring intravenous dextrose	>72 hours or requiring >10-12 mg/kg/min dextrose
Queensland[124]; babies at risk	<2.6 if <48 hours, <3.3 if >48 hours, <4.0 if known hypoglycaemic disorder	>2.6 if <48 hours, >3.3 if >48 hours, >4.0 if known hypoglycaemic disorder	If 1.5-2.5 mmol/l, buccal 40% dextrose gel 0.5 mL/kg with more feeds. If <1.5 mmol/L, glucagon 200 µg/kg	Intravenous 10% dextrose 1-2 mL/kg bolus and infusion 60 mL/kg/day (4.2 mg/kg/min)	Another intravenous dextrose bolus 1 mL/kg	24 hours	Until ≥2.6 mmol/L for 24 hours in first 48 hours or ≥3.3 mmol/L after 48 hours or ≥4.4 mmol/L after 6 hour fast if known hypoglycaemic disorder	Persistent or recurrent despite ≥8 mg/kg/min intravenous dextrose, clinical features, or family history

.AAP, American Academy of Paediatrics; ABM, Association of Breastfeeding Medicine; BAPM, British Association of Perinatal Medicine; NS, not specified; WHO, World Health Organization.

with no risk factors (see section on long term consequences below).[77]

Fourthly, consensus is lacking on the appropriate length and frequency of testing for blood glucose in infants at risk of hypoglycaemia (table 3). Most guidelines recommend screening for 8-24 hours after birth,[70 78] although most infants with risk factors who then require intravenous dextrose are identified from the first or second blood glucose test.[75] Further research is needed to determine how long and how often infants at risk of hypoglycaemia should be monitored with intermittent testing of blood glucose to detect infants with hypoglycaemia whose long term outcomes can be improved with treatment.

Newer approaches to monitoring

Measurement of glucose concentrations in plasma by laboratory chemical analyser or whole blood by gas analyser remains the gold standard for detection of hypoglycaemia. A renewed focus on developing better approaches to continuous monitoring of tissue glucose has been reported, however, potentially allowing blood sampling to be used for confirmatory testing rather than screening. Measurement of tissue glucose in neonates is challenging because of the low operating range required, and the potential for rapidly changing blood glucose concentrations, which can make calibration of tissue readings difficult.[79]

In adults and children, a range of commercial amperometric filament sensor devices are available for continuous monitoring of glucose in subcutaneous tissue. The sensors measure electric current generated by the oxidation of glucose from the interstitial fluid when a voltage is applied. The sensors require a barrier membrane to limit access of glucose to the filament because of the limited oxygen availability,[79] resulting in a relatively long wet-in phase before a reading can be obtained, usually two hours, and optimal function might not be achieved for 4-6 hours. Build up of biofilm on the sensor membrane also makes the devices susceptible to drift. Although drift has not been formally quantified in neonates, it could be substantial relative to the lower glucose operating range. Common drug treatments, such as paracetamol, can also contribute to drift in some devices.

Another limitation of subcutaneous sensors is their dependence on diffusion of glucose from the vascular compartment to the interstitial fluid, and equilibration times could be up to 30 minutes when blood glucose concentration is falling.[80] Calibration during this physiological lag phase will increase negative bias in tissue glucose concentrations, potentially leading to unnecessary intervention.

Although the use of subcutaneous amperometric sensors in neonatal intensive care is increasing, none of the current systems has been designed for neonates. Drift, physiological lag, and the inherent noise of the sensor result in poor point accuracy, with 95% limits of agreement of at least ±1 mmol/L.[81 82] These large errors relative to the target blood glucose concentrations in neonates makes clinical interpretation difficult. Trend alarms might be more useful for predicting when blood glucose concentrations are most likely to be out of range. Trend monitoring of current commercial devices is not well suited to neonates, however, requires additional clinical judgment, and performance has not been fully validated, although such studies are underway.[83] New generation adult and paediatric subcutaneous sensors are designed to be used without calibration, but whether the factory set algorithms will improve or worsen performance in neonates, given their different transitional physiology, is not clear.

For research, sensor error can be minimised by retrospective recalibration of the raw current through all measured blood glucose concentrations.[84] This approach also allows for estimation of glucose concentrations <2.2 mmol/L (40 mg/dL), the lower limit of real time display for most devices. One promising technology in development is the glucose spectrometer, which uses the distinct infrared absorption pattern of glucose to measure tissue glucose.[85] Miniaturisation of narrow wavelength light emitting diodes that can act as emitters and detectors has allowed development of low cost wearable devices in a form suitable for neonates. In contrast with subcutaneous sensors which measure glucose in interstitial fluid, glucose spectrometers measure glucose mainly in blood in the underlying tissue, thereby avoiding problems of drift and physiological lag. In a proof of concept study, 93% of spectrometer estimated blood glucose concentrations were within the Clark error grid clinically acceptable range (sections A and B of the grid).[85]

Long term consequences

The rationale for screening and treatment for neonatal hypoglycaemia is the prevention of brain injury. Low quality evidence suggested that severe, prolonged hypoglycaemia can result in major damage and even death, although many infants had comorbid conditions, which might have affected the outcomes.[2 3 86] In children with persistent hyperinsulinaemia, poor neurological outcomes were common, and were seen more often in those who had more severe hypoglycaemia or seizures, or when delays in detection and treatment occurred.[3]

A meta-analysis of older and lower quality studies (six studies, 1657 children) reported similar odds of combined neurodevelopmental impairment from age two and five years in children who did and did not have neonatal hypoglycaemia (definitions ranged from <1.1 mmol/L to 2.6 mmol/L; odds ratio 1.16, 95% confidence interval (CI) 0.86 to 1.57).[4] The meta-analysis also reported that those who had neonatal hypoglycaemia were more likely to have

neurodevelopmental impairment when assessed at age 6-11 years (two studies, 54 children; odds ratio 3.62, 1.05 to 12.42).

More recent evidence suggests that even mild, brief, and asymptomatic neonatal hypoglycaemia could be associated with poorer outcomes, although the evidence is conflicting and causal relations are uncertain. A large secondary analysis of a randomised trial cohort of 1194 late preterm and term infants, born at risk of neonatal hypoglycaemia and screened and treated if hypoglycaemia was detected, nevertheless found that neonatal hypoglycaemia (<2.6 mmol/L) was associated with poorer neurodevelopment at age two years (adjusted risk ratio 1.28, 95% CI 1.01 to 1.60), and this risk was greater after more severe hypoglycaemia (<2.0 mmol/L; adjusted risk ratio 1.68, 1.20 to 2.36).[77] Similarly, a large population based cohort study of 101 060 infants reported that moderate neonatal hypoglycaemia (<2.2 mmol/L) was associated with an increased risk of any neurological and neurodevelopmental impairment at age 2-6 years (adjusted risk ratio 1.48, 1.17 to 1.88).[87]

Evidence from randomised trials is limited and conflicting. Two trials of the use of prophylactic dextrose gel to reduce the incidence of hypoglycaemia in infants at risk both reported that infants randomised to receive the dextrose gel had a lower risk of neonatal hypoglycaemia (<2.6 mmol/L, relative risk 0.79, 95% CI 0.64 to 0.98, n=416 and 0.88, 0.80 to 0.98, n=2149).[88 89] At age 2 years, both studies reported no difference between the groups in the main outcome of risk of neurosensory impairment.[90 91] The first trial, however, reported a trend towards improved secondary outcomes related to language, motor, and executive function in the dextrose gel group who had less hypoglycaemia,[90] whereas the second trial reported worse language, motor, and cognitive function[91] in the dextrose gel group.

These different findings might be in part because the characteristics of the infant, characteristics of hypoglycaemia (eg, length, severity, and recurrence), availability of alternative brain substrates, and even treatment all interact to determine developmental outcomes. For example, including infants with comorbid conditions, often hypoxia-ischaemia, might confound relations between neonatal hypoglycaemia and later outcomes.[55 92] In contrast, the longer term consequences of neonatal hypoglycaemia are more easily detectable in cohorts of otherwise healthy infants with no acute neonatal illnesses.[77 87] Infants who have neonatal hypoglycaemia at 12-24 hours after birth might also be more at risk of poorer neurodevelopment than those who have neonatal hypoglycaemia in the first 12 hours or after 24 hours because of low levels of neuroprotection from alternative sources of energy, such as lactate and ketone bodies.[13] No clear evidence exists, however, that the timing of neonatal hypoglycaemia affects longer term outcomes.[87]

Recent data also raise the question of whether transitional hypoglycaemia, particularly if mild, is actually a marker of physiological instability associated with adverse development, rather than a cause, and distinguishing these possibilities is challenging. The Children with Hypoglycaemia and Their Later Development (CHYLD) prospective cohort study reported that in 477 moderate to late preterm and term infants born at risk of neonatal hypoglycaemia, those who had hypoglycaemia (<2.6 mmol/L) were more likely to have executive dysfunction (adjusted risk ratio 2.32, 95% CI 1.17 to 4.59) and poor visual-motor function (adjusted risk ratio 3.67, 1.15 to 11.69) at age 4.5 years,[8] but these poorer outcomes did not persist at age 9-10 years (480 children; adjusted risk ratio 0.95, 0.78 to 1.15).[54] These at-risk children had similarly high rates of poor educational achievement, regardless of neonatal hypoglycaemia, suggesting that the main reason for being at risk, rather than the hypoglycaemia itself, might have contributed to their developmental trajectory. This interpretation could also explain why in the large randomised trial of dextrose gel prophylaxis, a treatment that reduced the risk of hypoglycaemia did not seem to reduce the risk of later adverse outcomes,[91] despite hypoglycaemia being associated with poorer neurodevelopment in the same participant cohort.[77]

Treatment

Feeding

Initial treatment of hypoglycaemia is usually more feeding, but evidence to support this approach as the only treatment is lacking. Breastfeeding is important for all infants, but in the first days after birth, when hypoglycaemia is most common, breast milk volumes are small[93 94] and lactose and therefore calorie content is low.[95] This effect could explain why in healthy term infants, little or no increase in blood concentrations of glucose after breastfeeding is seen in the first 48 hours after birth.[96] In this prospective cohort study of 62 healthy term infants, the increase in blood glucose concentrations after feeding in the first five days was greater after prolonged breastfeeding (>30 min) and feeding from both breasts.

In another cohort study of 227 infants with hypoglycaemia in the first 48 hours, small increases in blood glucose concentrations (about 0.2 mmol/L) after formula feeding or dextrose gel (see section on dextrose gel below) were reported but not after expressed breast milk or breastfeeding.[93] Breastfeeding was associated with a reduced risk of recurrent hypoglycaemia, however, perhaps by non-milk mechanisms (ie, stimulation of secretion of gastrointestinal hormones, such as gastrin and cholecystokinin).[97] Another matched cohort study (33 infants in each group) also reported greater increases in blood glucose concentrations in infants

with hypoglycaemia given dextrose gel together with donor milk or formula (about 1 mmol/L) than in those given dextrose gel with breastfeeding (about 0.4 mmol/L).[98] Although expression of breast milk either before or after birth is often recommended to provide milk for babies at risk of or who develop neonatal hypoglycaemia, no evidence exists that this practice alters neonatal blood glucose concentrations or the risk of hypoglycaemia.[99 100] A practical approach to feeding the infant with hypoglycaemia might therefore be to encourage breastfeeding, including for longer periods and from both breasts, rather than expressing breast milk, and consider adding dextrose gel, donor milk, or infant formula.

Dextrose gel

Dextrose gel is usually given to infants with hypoglycaemia as 0.5 mL/kg of 40% dextrose gel (200 mg/kg), rubbed into the buccal mucosa, followed by a feed. Compared with feeding alone, dextrose gel reduced the risk of treatment failure, intravenous treatment, and admission to the neonatal intensive care unit for treatment of hypoglycaemia, while increasing successful breastfeeding.[101] The gel seems to have no adverse effects, including on developmental assessment at ages 4.5 and 9-10 years, and is well accepted and tolerated by infants, their families, and healthcare providers.[65 102–104] Dextrose gel is inexpensive (a few US$ per dose), can be made up in a hospital pharmacy, and does not require refrigeration, so it can potentially be available in many healthcare settings. The benefits might be even greater in lower income settings.[105] The gel is now widely recommended as a first line treatment for late preterm and term infants, although no data exist on its role, if any, in infants born at earlier gestations (table 3).[106–109] Treatment can be repeated as needed, but most guidelines recommend an upper limit on the number of doses (usually two or three per episode of hypoglycaemia, and a maximum of five or six doses in 48 hours). This approach reflects the need for further review and possibly escalation of treatment for an infant whose hypoglycaemia is not resolving, rather than any known risk of repeated doses of gel.

Oral sucrose

In settings where resources are limited and dextrose is not readily available, sucrose has been used to prevent or treat neonatal hypoglycaemia, but high quality evidence to support its effectiveness is lacking. In principle, this approach is likely to be less immediately effective than giving dextrose. Because sucrose is a disaccharide of glucose with fructose, it requires digestion into these component sugars before uptake across the intestinal mucosa into the portal system, and therefore changes in concentrations of blood glucose can be delayed or even absent. Potentially consistent with this effect, an Indian randomised trial (n=425) of oral sucrose solution (0.8 mL/kg of 24% solution, or 192 mg/kg), given with a feed soon after birth to infants at high risk of hypoglycaemia, did not alter blood glucose concentrations up to age six hours compared with feeding alone.[110] In another trial in Thailand, however, 80 infants with stable hypoglycaemia born small for gestational age at 32-36 weeks' gestation were randomised to receive intravenous dextrose or expressed breast milk enriched with sucrose in similar calculated doses. No difference between the groups was seen in blood glucose concentrations six hours after treatment, or in the incidence of recurrent hypoglycaemia.[111]

Intravenous dextrose

If feeding and dextrose gel do not reverse hypoglycaemia, intravenous dextrose is usually required. Recommended initial infusion rates (4-6 mg/kg/min or 60-90 mL/kg/day of 10% dextrose, table 3) are similar to neonatal glucose requirements (normally produced endogenously), with increases in volume or concentration, or both, as needed to maintain euglycaemia. Greater uncertainty exists over the use of an initial bolus as well as continuous infusion. A bolus of 1-2 mL/kg of 10% dextrose is quick and easy to administer, and achieves a prompt increase in blood glucose concentrations.[112] An association between high and unstable glucose concentrations after neonatal hypoglycaemia and adverse neurodevelopmental outcomes has been reported,[55] however, and infants treated with intravenous dextrose, rather than dextrose gel, formula, or breast milk, were more likely to have high and unstable glucose concentrations.[56] This finding prompted recommendations to limit the use of an initial bolus of dextrose to infants with severe or symptomatic hypoglycaemia.[113] One before-and-after cohort study of 277 infants reported a graded approach to both the use of a bolus and the rate of infusion, depending on the severity of the initial hypoglycaemia. The authors reported that the graded approach improved stability of blood glucose concentrations as well as shortened the stay in the neonatal intensive care unit, and reduced costs without changing the time to achieving normoglycaemia.[114] More trials of this and similar approaches are warranted.

Glucagon

For infants whose glucose concentrations are difficult to stabilise with intravenous dextrose, or who have repeated episodes of hypoglycaemia, other treatments should be considered. Glucagon is a peptide hormone that counteracts the effects of insulin by stimulating production of hepatic glucose. Thus glucagon is a potentially useful intervention for infants when insulin secretion is inadequately suppressed because it targets the underlying pathophysiology of the hypoglycaemia. A recent systematic

review of the use of glucagon for treatment of hypoglycaemia included seven studies (none randomised trials) with a total of 348 infants.[115] The review reported that glucagon probably increased blood glucose concentrations by about 2.3 mmol/L after 1-2 hours, and that ≥80% of infants treated achieved euglycaemia within four hours, but recurrent hypoglycaemia was common (55%). The certainty of evidence was very low and few data on adverse effects or long term outcomes were available. The effects did not seem to change with the dose used or the route of administration (intramuscular or intravenous bolus or infusion). Although glucagon has be given subcutaneously or intranasally in adults for emergency management of hypoglycaemia, these forms of administration have not been reported in neonates.

So far, the evidence of the role of glucagon in the management of neonatal hypoglycaemia is inadequate. Glucagon is potentially useful as a short term option, however, in circumstances where alternatives are not immediately available (eg, while arranging transfer to the neonatal intensive care unit, or when intravenous access is difficult to establish). Glucagon might also be useful to reduce the need for admission to the neonatal intensive care unit[116] or as an adjunct treatment to reduce the intensity of secondary interventions (eg, length of intravenous infusion).

Glucocorticoids

Cortisol is a naturally occurring corticosteroid that has numerous actions on glucose metabolism, mainly by suppressing the peripheral actions of insulin and stimulating gluconeogenesis. Although secretion of cortisol is normally stimulated by physiological stress, including hypoglycaemia, neonates with hyperinsulinaemic hypoglycaemia might not generate an adequate cortisol counter-regulatory response.[117 118] Replacement doses of cortisol are sometimes recommended if this effect is suspected.

Other treatments

Because of the uncertainty of the extent to which dextrose provides neuroprotection after hypoglycaemia and the potential for dextrose infusions to increase secretion of insulin, alternative approaches to the treatment of neonatal hypoglycaemia are being considered, including drug treatments aimed at promoting β cell adaptation. Diazoxide activates the ATP sensitive potassium channel, thereby increasing β cell membrane potential, which limits secretion of insulin. Low certainty evidence suggests that early commencement of short courses of diazoxide in at-risk infants with hypoglycaemia might promote glycaemic stability and reduce the need for intravenous dextrose,[119] with further trial evidence awaited.[83]

Future directions

Some of the many challenges to the research required to provide a robust evidence base for the management of neonatal hypoglycaemia include the high frequency of both risk factors and low glucose concentrations in apparently healthy infants, and the lack of reliable clinical markers of neuroglycopenia. Also, intervention studies need to be adequately powered and include long term follow-up (at least to school age) to determine clinically relevant neurodevelopmental outcomes. Some research priorities might include:

- Exploring the role of neuroprotective substrates other than glucose to stabilise neuronal metabolism without exacerbating superoxide production
- Identifying clinically applicable markers of neuroglycopenia
- Randomised trials of different thresholds for diagnosis and treatment of hypoglycaemia
- Developing new glucose monitoring techniques, including randomised trials investigating the role of glucose measurements in tissues in the screening and treatment of neonatal hypoglycaemia
- Determining which infants might benefit from screening for neonatal hypoglycaemia, including those with no commonly identified risk factors (eg, infants born large for gestational age, exposed to antenatal corticosteroids, and after caesarean section)
- Investigating effective preventive strategies for infants at risk that help reduce neonatal hypoglycaemia and improve later neurodevelopment
- Developing less invasive treatment approaches that look at the underlying pathophysiology of transitional hypoglycaemia and avoid the need for intravenous treatment and admission to the neonatal intensive care unit
- Randomised trials of different approaches to intravenous glucose treatment, including the role of an initial bolus
- Determining neurodevelopmental outcomes after asymptomatic hypoglycaemia in infants with no risk factors
- Exploring parental preferences for prevention, detection, and treatment, including perceptions of the balance of risks and benefits.

Conclusions

Neonatal hypoglycaemia is common, and could potentially be the most common cause of preventable brain injury in the newborn. For this reason, screening of infants at risk and treating low concentrations of glucose is standard practice.

In recent years, progress has been made in understanding the pathophysiology of the neonatal

metabolic transition and mechanisms of brain injury. Also, some progress in the development of a new non-invasive treatment (dextrose gel) has been made and in describing long term neurodevelopmental outcomes, particularly in infants at risk. Current approaches to detection are invasive, however, and do not meet the standard criteria for an effective screening programme. Thresholds for diagnosis are confused, and optimal treatment strategies to avoid further harm are uncertain. The effects of mild, transient hypoglycaemia and its treatment on later neurodevelopment are poorly understood. Growing evidence highlighting the potential for harm as well as benefit with all interventions, including screening and treatment, might partially explain why interpretation of the evidence has been so challenging.

More than 20 years ago, Cornblath et al noted that "The definition of clinically significant hypoglycaemia remains one of the most confused and contentious issues in contemporary neonatology."[120] The report of a National Institutes of Health workshop published in 2009 concluded that "There has been no substantial evidence-based progress in defining what constitutes clinically significant...neonatal hypoglycaemia... Monitoring for and prevention and treatment of neonatal hypoglycaemia remain largely empirical."[121] Considerable research effort will be required to avoid these statements being just as applicable in another 20 years.

QUESTIONS FOR FUTURE RESEARCH

- ⇒ What are the optimal thresholds for diagnosis and treatment of neonatal hypoglycaemia and for which infants?
- ⇒ Who should be tested for neonatal hypoglycaemia, how should they be tested, and for how long?
- ⇒ How is hypoglycaemia best prevented and treated?
- ⇒ Does mild neonatal hypoglycaemia or its treatment, or both, influence later neurodevelopment?

PATIENT INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

AUTHOR AFFILIATIONS

[1]Liggins Institute, University of Auckland, Auckland, New Zealand
[2]Department of Paediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand
[3]Te Whatu Ora Health New Zealand, Te Toka Tumai, Auckland, New Zealand
[4]Te Whatu Ora Health New Zealand, Counties Manukau, Auckland, New Zealand

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ORCID iD
Jane E Harding http://orcid.org/0000-0003-2697-1422

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