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Describing hypoglycemia - definition or operational threshold?

Paul J. Rozance, MD[Assistant Professor] and
Department of Pediatrics, University of Colorado School of Medicine, University of Colorado Denver, Aurora, Colorado USA

William W. Hay Jr., MD[Professor]
Department of Pediatrics, Co-Director, Colorado Clinical Translational Science Institute (Director, Child and Maternal Health Program), Scientific Director, Perinatal Research Center, University of Colorado School of Medicine, University of Colorado Denver, Aurora, Colorado USA

Abstract

Severe glucose deficiency leads to cerebral energy failure, impaired cardiac performance, muscle weakness, glycogen depletion, and diminished glucose production. Thus, maintenance of glucose delivery to all organs is an essential physiological function. Normal term infants have sufficient alternate energy stores and capacity for glucose production from glycogenolysis and gluconeogenesis to ensure normal glucose metabolism during the transition to extrauterine life and early neonatal period. Milk feedings particularly enhance glucose homeostasis. Energy sources often are low in preterm and growth restricted infants, who are especially vulnerable to glucose deficiency. Plasma glucose concentration is the only practical measure of glucose sufficiency, but by itself is a very limited guide. Key to preventing complications from glucose deficiency is to identify infants at risk, promote early and frequent feedings, normalize glucose homeostasis, measure glucose concentrations early and frequently in infants at risk, and treat promptly when glucose deficiency is marked and symptomatic.

Keywords

glucose; hypoglycemia; fetus; neonate; insulin; neurodevelopment; operational thresholds

Fetal glucose metabolism

Throughout gestation, maternal glucose provides all of the glucose for the fetus via facilitated diffusion across the placenta according to a maternal-to-fetal glucose concentration gradient.[1] Thus, glucose production in the fetus normally is non-existent or very low, although the enzymes for gluconeogenesis are present by the third month of gestation. If fetal glucose requirements cannot be met because of maternal hypoglycemia or placental insufficiency, the fetus can use alternate substrates, such as ketone bodies derived from beta-oxidation of fatty acids. With prolonged low glucose supply, the fetus develops its own glucose production, first by glycogenolysis and after more extended periods of glucose deficiency by gluconeogenesis, as well as complex changes in glucose metabolism, these

Addresses for communications: William W. Hay, Jr., MD, University of Colorado Denver F441, Perinatal Research Center, 13243 East 23rd Avenue, PO Box 6508, Aurora, CO 80045 USA, Telephone: 303-724-1600, Fax: 303-724-0898, bill.hay@uchsc.edu.

being at the expense of fetal growth and some of which produce variable and often unpredictable metabolic changes in neonatal glucose metabolism.

Fetal glucose deficiency and development of abnormal glucose homeostasis

Despite the prevailing low glucose and insulin concentrations in the fetus with intrauterine growth restriction (IUGR), glucose uptake and utilization are maintained by augmented insulin and glucose sensitivity to promote glucose uptake into tissues,[1,2] mediated at the cellular level by increased expression of glucose- and insulin-responsive glucose transporters.[3] Chronic fetal glucose deficiency in IUGR fetuses leads to cell cycle arrest of the pancreatic β-cells, fewer β-cells, and reduced capacity of the fetal pancreas to secrete insulin.[4,5] IUGR offspring also develop an apparent “central” or hepatic resistance to insulin, characterized by a block in proximal insulin signaling in hepatocytes, which leads to increased PEPCK (phosphoenolpyruvate carboxykinase), the rate limiting enzyme for gluconeogenesis, and significant rates of hepatic glucose production (HGP).[6] These metabolic adaptations in the IUGR fetus lead to a propensity for persistent hyperglycemia that is not easily reversed by simply reducing glucose supply. Chronic glucose deprivation in the IUGR fetus, therefore, produces competing metabolic changes of increased capacity for glucose utilization and a tendency to hypoglycemia vs. a propensity for glucose production and hyperglycemia. Thus, glucose metabolism and circulating glucose concentrations in IUGR/SGA neonates often are unpredictable.

Glucose excess and development of abnormal glucose homeostasis

Similarly, constant, marked, and chronic hyperglycemia during gestation, as sometimes occurs in insulin dependent pregnant diabetic women, can diminish insulin production and produce peripheral insulin resistance and glucose intolerance.[7] In contrast, episodic hyperglycemia in the fetus, such as the marked meal associated hyperglycemia that occurs in gestational diabetics who produce macrosomic (obese) infants, tends to up-regulate insulin secretion and glucose disposal, particularly in response to a sudden increase in glucose concentration.[8] This condition sets up the neonate for rapid insulin secretion and rebound hypoglycemia, often to severely low levels, as can occur following intravenous glucose bolus infusions. Just as with the IUGR infant, therefore, predicting postnatal glucose metabolic rates or circulating glucose concentrations in infants of diabetic mothers is not straightforward.

Postnatal glucose metabolism

At birth the infant is removed abruptly from its glucose supply and blood glucose concentration decreases; this phenomenon is ubiquitous among mammals and is a normal physiological function that is essential for activating glucose production by the neonate. Several hormonal and metabolic changes at birth facilitate adaptations that provide glucose to replace the supply previously received via the placenta. Induction of HGP begins shortly before term birth and is augmented after birth by increased secretion of glucagon and glucocorticoids that trigger gene transcription of PEPCK and activate gluconeogenesis.[9,10] Catecholamine concentrations increase markedly at birth and together with glucagon activate hepatic glycogen phosphorylase and glycogenolysis. The perinatal surge in fetal cortisol secretion stimulates hepatic glucose-6-phosphatase activity and hepatic glucose release. Increased catecholamines also stimulate lipolysis, providing energy (ATP) and co-factors (NADPH) that enhance activity of enzymes responsible for gluconeogenesis.

Normal glucose metabolism in newborn infants

Maintenance of glucose homeostasis depends on the balance between hepatic glucose output and peripheral glucose utilization. Steady state glucose utilization rates in term neonates are 4 to 6 mg/min/kg, about half the values of 8–9 mg/min/kg that occur at earlier gestational ages in both the fetus and preterm infant of the same gestational age.[1] Peripheral glucose utilization may increase during hypoxia due to the inherent inefficiency of anaerobic glycolysis, hyperinsulinemia which increases glucose uptake by insulin-sensitive tissues, and cold stress which increases metabolic rate via sympathetic nervous system activity and thyroid hormone secretion. Once normal feedings are established, glycerol and amino acids continue to fuel gluconeogenesis. Galactose derived from hydrolysis of milk sugar (lactose) in the gut increases hepatic glycogen production and allows for sustained between-feeding hepatic glucose release from glycogen breakdown. Feedings also induce production of intestinal peptides, or incretins, that promote insulin secretion. Insulin decreases hepatic glucose production and increases glucose utilization for energy production and storage as glycogen. If rates of glycogenolysis and gluconeogenesis do not match the rate of glucose utilization because of failure of hormonal control mechanisms or reduced alternate substrate supply, disturbances of glucose homeostasis develop, including hypoglycemia.

Hypoglycemia – current state of the art and science

Glucose concentration is the most frequently measured laboratory value in neonatal medicine, presumably to diagnose and treat low glucose concentrations, or “hypoglycemia.” Unfortunately, there still is no research basis or consensus regarding the definition of neonatal hypoglycemia, who is at risk and when and under what circumstances, when screening should be performed, what is optimal management, what is the level and duration of neonatal hypoglycemia that might cause neurological injury with permanent sequelae, or what is the outcome of common forms of neonatal hypoglycemia.[11] No single concentration of plasma glucose is always associated with the appearance of clinical signs or causation of cerebral injury.[12] As a result, “The definition of clinically significant hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology.”[13]

Definition of Hypoglycemia

Stedman’s Medical Dictionary defines hypoglycemia as an abnormally diminished content of glucose in the blood, begging the questions: Compared to what? How diminished? For how long? In relation to what other conditions or problems, such as brain blood flow, hematocrit/hemoglobin concentration, oxygen level, prior or concurrent hypoxia/ischemia, sepsis, etc.? “Abnormally” also requires discrimination between statistical and desirable concentrations, both ill-defined terms. The term “hypoglycemia” also requires definition with respect to glucose utilization by different cells, tissues, and organs, some of which are apparently more vulnerable than others to glucose deprivation.

Historical and current definitions of hypoglycemia—confusion and contradiction

Hypoglycemia was defined by studies as early as 1937 as “mild”, ~2.2–3.3 mmol/L (40–60 mg/dL), “moderate”, ~1.1–2.2 mmol/L (20–40 mg/dL), and “extreme”, <1.1 mmol/L (<20 mg/dL).[14] A variety of surveys over the past 70 years have indicated that even extremely low (0–0.5 mmol/L or 0–10 mg/dL) glucose concentrations are of limited significance, as they occur with and without clinical manifestations, usually are transient, and are easily corrected. More recently, other authors in “definitive” textbooks have provided different but variable definitions of hypoglycemia: <2 mmol/L blood (<36 mg/dL), Kalhan and Parimi;[15]

<2.2 mmol/L blood (<40 mg/dL), Ogata;[16] and <2.0–3.3 mmol/L (<36–40 mg/dL) blood, <2.2–2.5 mmol/L (<40–45 mg/dL) plasma, McGowan and Hay.[17] A survey in the United Kingdom found that medical practitioners varied considerably in their definition of "hypoglycemia" with only limited correlation to published definitions.[18] Two other authors, without any experimental data, even suggested raising the lower limit of normal to >3.3 mmol/L (>60 mg/dL), into the "normal" range of 3.9–5.6 mmol/L (70–100 mg/dl), claiming that there is no evidence to support the hypothesis that the newborn has a unique physiologic adaptation to low blood glucose levels.[19] This suggestion, which more appropriately applies to neonates and infants with hyperinsulinism, remains untested.

Operational Threshold

In response to such variable definitions, Cornblath et al. developed the concept of an "Operational Threshold," defined as "that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in the literature." [13] An Operational Threshold is distinguished from a "treatment target", which is somewhat higher, and a "concentration at which organ damage is known to occur," which is somewhat lower. An "operational threshold" is an indication for action and is not diagnostic of a disease or predictive of adverse neurological sequelae by itself. The Operational Threshold still focuses, however, on individual glucose concentrations and does not clarify for how long or how far below the Operational Threshold glucose concentrations should be before starting treatment.

Evidence-based approaches to defining hypoglycemia

Others have attempted to use evidence-based approaches to define lower limits of normal glucose concentrations, including the plasma glucose concentrations found in normal human fetuses, >3 mmol/L,[20] and the plasma glucose concentrations observed in relatively large populations of healthy full-term infants, >1.7 mmol/L (>30 mg/dL) in the first 24 hours of life and > 2.5 mmol/L (>45 mg/dL) after 24 hours.[21] Such data depend on the physiology of the infant's adaptation to postnatal life, the character of the patient population (e.g., proportion of high-risk infants), and the feeding practices at the time the data were collected. Still others have noted from animal studies that plasma glucose concentration needs to be markedly less than normal for two or more hours with evidence of profound neurological pathophysiology (e.g., an isoelectric EEG) before there is irreversible neuronal injury.[22]

Clinical approaches to defining hypoglycemia

Hypoglycemia also can be defined as the glucose concentration in a neonate that is associated with clinical signs that resolve when glucose is administered. Such signs are non-specific, however, and may not be noticed initially. Attempts to quantify physiological glucose sufficiency or insufficiency have included magnetic resonance scans and measurements of cortical electrical activity and brain glucose uptake rates. Such approaches are difficult to perform and by themselves to not prove the singular role of glucose when abnormalities using these methods are identified.

Importance of normal glucose concentrations in newborn infants

Human newborns are unique among mammals in having an extremely large brain relative to body size. Whole body glucose disposal correlates with brain weight and the brain requires glucose for its normal function. Furthermore, cerebral glucose utilization depends on arterial plasma glucose concentration. There is little glucose or glycogen stored in the fetal or neonatal brain, and very preterm and IUGR infants have little alternate substrates. Polycythemia, hyperviscosity, hypotension, and decreased cardiac output, relatively

common problems in both IUGR and preterm infants, reduce cerebral plasma flow and glucose delivery to the brain. Concurrent hypoglycemia adds to hypoxic-ischemic neuronal injury, and vice versa, although there still is no evidence to indicate whether early detection of hypoglycemia in such infants, such as in the delivery room, could lead to earlier treatment and modify subsequent neurological outcome. Also, repeated low glucose concentrations, <2.6 mmol/L (<47 mg/dL), in preterm infants were associated with delayed neurological development at 18 months of age, although this study had several methodological complications and the difference between infants with normal and repeated low glucose concentrations was considerably diminished at 7.5–8 yrs.[25]

Complications of Hypoglycemia

Symptomatic hypoglycemic infants, primarily those with severe, protracted, and recurrent neurological conditions such as seizures and coma, plus plasma glucose concentrations of zero to 1.1 mmol/L (0–20 mg/dL) for several hours or more, have a poor prognosis, with abnormalities ranging from learning disabilities to cerebral palsy and persistent or recurrent seizure disorders, as well as mental retardation of varying degrees. Despite such evidence, the prognosis of most cases of neonatal hypoglycemia is not reliably defined. Follow up data often are limited, hard to get, and studies often are retrospective. Data linking plasma glucose concentrations with long-term neurological outcomes have been limited by lack of non-hypoglycemic control infants, the possibility that other conditions were responsible, and inclusion of only a small number of hypoglycemic but asymptomatic infants.[26] Furthermore, when hypoglycemia is part of underlying processes, it often is difficult to distinguish whether an abnormal outcome results from hypoglycemia or from the underlying process. Nevertheless, several studies provide some evidence for adverse but quite variable outcomes associated with neonatal hypoglycemia.

IUGR/SGA infants

Duvanel, et al. studied the long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in preterm SGA infants, finding that 72% of the SGA infants developed hypoglycemia (<2.6 mmol/L or 47mg/dl).[27] Those with recurrent neonatal hypoglycemia had smaller head circumferences at 18 months of age and lower scores on specific psychometric scores at five years. Importantly, recurrent hypoglycemia was a more predictable factor for long-term effects than the severity of a single hypoglycemic episode.

Infants of diabetic mothers (IDMs)

In IDM's, neonatal hypoglycemia has been associated with a slightly higher incidence of long-term neurological dysfunction related to minimal brain dysfunction/deficits in attention, motor control, and perception compared with non-hypoglycemic, non-IDM control infants.[28] Specific data on the duration of hypoglycemia were not provided for the group of hypoglycemic infants.

Large for gestational aged (LGA) infants without maternal diabetes

Neurodevelopmental outcome in healthy but hypoglycemic, term, large for gestational aged (LGA) infants who are not IDMs is controversial. One study noted that "Transient mild hypoglycaemia in healthy, term LGA newborns does not appear to be harmful to psychomotor development at the age of 4 years." [29] In contrast, a recent study noted a high incidence (16.2%) of hypoglycemia in admitted, non-IDM LGA full term infants; 1.3% of those had seizures as the primary clinical manifestation.[30] As reported, though, the timing and duration of the low glucose concentrations after birth and in relation to clinical signs

were not described. Furthermore, many mothers of LGA infants are obese and while they might not have overt gestational diabetes, they often do have borderline glucose intolerance.

Clinical Signs ("Symptoms") of Hypoglycemia

The most common, but least specific, signs associated with hypoglycemia can be seen in normal infants. They include mild to moderate changes in levels of consciousness, such as stupor or lethargy, tremulousness, and irritability. Such signs usually are relatively quickly and easily reversed with normalization of glucose supply and plasma concentration. With more serious hypoglycemia, coma and seizures occur, dependent on the duration, repetitive occurrence, and severity of hypoglycemia. Other signs are more variably present, including respiratory depression or actual apnea leading to cyanosis, hypotonia, limpness, and inactivity, a high-pitched cry, poor feeding after previously feeding well, and hypothermia. The more serious signs usually occur late in severe and protracted cases of hypoglycemia and are not easily or rapidly reversed with glucose replacement and normalization of plasma glucose concentrations. Variability in clinical signs is increased by the variable presence of alternate substrates,[31] metabolic adaptations that affect glucose production and utilization**,** [3,32] and highly variable physiology (hematocrit, plasma flow, hypoxia-ischemia, etc.).

Treatment of Hypoglycemia

Because no single concentration of plasma glucose is always associated with the appearance of clinical signs or causation of cerebral injury, treatment should be based on a flexible approach guided by clinical assessment and not solely on plasma glucose concentration. Anticipation and prevention are the key elements of intervention and management, requiring early identification of an infant at risk and institution of prophylactic measures to prevent the occurrence of hypoglycemia. In infants in whom hypoglycemia does occur, the treatment goals are to promptly return the glucose concentration to normal values and maintain concentrations within the normal range.[11,13]

Guidelines for Glucose Monitoring

Neonatal glucose concentrations decrease during the first hour or two after birth, reaching a nadir around two hours after birth, and then increase to higher and stable neonatal concentrations. There are limited data on optimal timing and intervals for glucose concentration screening. No studies have demonstrated harm from such periods of transient asymptomatic hypoglycemia during this normal postnatal period of physiological glucose homeostasis.[33]

Infants at significant risk for hypoglycemia (Table 1) need to be monitored early and frequently, particularly in those with recurrent hypoglycemia, until they maintain normal before-feeding glucose concentrations through several fast-feed cycles. This admonition also should apply to all infants who do not feed well, either from breast or bottle. The period of "several" fast-feed cycles has not been defined rigorously and is practiced with considerable variability. The risk of not ensuring normal capacity for glucose homeostasis is that recurrent but intermittent hypoglycemia from serious underlying pathological conditions will be missed, particularly fatty acid oxidation disorders and persistent hyperinsulinism, which almost invariably are associated with serious risk to life and long term adverse neurological outcomes.

Neonatal hypoglycemia in IDMs can occur as early as less than one hour but usually by 12 hours of birth, while preterm and IUGR/SGA infants may be vulnerable to neonatal hypoglycemia for longer postnatal periods.[34,35,36] At risk infants, therefore, should be screened for neonatal hypoglycemia with a frequency and duration related to specific risk

factors of the individual infant.[12] In contrast, healthy full-term infants born after an entirely normal pregnancies and deliveries and who have no clinical signs do not require monitoring of glucose concentrations. They should be fed early and regularly and with special assistance given to young, inexperienced, and unsupported (e.g., single) mothers. Breastfed infants commonly have lower glucose concentrations than infants fed formulas, but they also have higher ketone concentrations, indicating that such conditions are normal and that lower "normal" glucose concentrations (perhaps up to 0.5 mmol/L lower) ought to apply to breastfed infants.[31,33]

Complications and treatment of asymptomatic low glucose concentrations

Neonates with asymptomatic hypoglycemia usually have a normal neurodevelopmental outcome. As stated by the American Academy of Pediatrics Committee on Fetus and Newborn "No study has shown that treatment of a transiently low blood glucose level offers a better short-term or long-term outcome than the outcome resulting with no treatment…. Furthermore, there is no evidence that asymptomatic hypoglycemic infants will benefit from treatment…" [37] or from supplements such as water, glucose water, formula, or other fluids. [38] Management of hypoglycemia by feeding is widely used for asymptomatic hypoglycemia and usually is successful. Such infants still bear careful observation as the infant might appear normal but already have activated catecholamine secretion, which reduces gastric and intestinal peristalsis (even inducing emesis), preventing digestion of the lactose in the milk or formula and limiting its capacity, once hydrolyzed, to produce glucose and galactose for absorption and correction of glucose deficiency.

Guidelines for treatment of symptomatic, low glucose concentrations ("hypoglycemia")

More severe hypoglycemia that is associated with significant clinical signs and pathophysiology should be treated by the "minibolus" approach: 200 mg/kg or 2 mL of D10W [10% dextrose in water] IV over 5 minutes followed by a constant infusion of dextrose at 6–8 mg/min/kg.[39] A constant infusion of glucose, if at high enough rates (at least 6–8 mg/min/kg), works almost as well, producing normal glucose concentrations only 5–10 minutes later than those produced by the minibolus, and is preferable when treating an infant with suspected or proven hyperinsulinism, as excessive dextrose boluses, especially when they rapidly produce higher glucose concentrations, lead to rebound hypoglycemia. Too many boluses of glucose and too high a glucose infusion rate, especially with hyperinsulinism, can lead to excessive glucose utilization rates, persistent hyperinsulinism, and abnormal metabolism (metabolic acidosis, hypercarbia, high lactate concentrations, and, over time, fatty infiltration of organs and obesity). Rapid IV boluses of hypertonic dextrose solutions also might cause osmotic injuries: of note, 5% Dextrose = 278 mOsm/L (~isotonic); 10% Dextrose = 540 mOsm/L (hypertonic); 25% Dextrose = 2770 mOsm/L (very hypertonic).

Persistent Hypoglycemia

The worst neurological outcomes from low glucose concentrations occur in neonates and infants with persistent and recurrent severe hypoglycemia.[40] Persistent hypoglycemia bears the associated risks of serious metabolic conditions, particularly fatty acid oxidation disorders (FAODs) and hyperinsulinism. FAODs are caused by genetic defects in the capacity to take up into the mitochondria and oxidize long chain fatty acids, leading to rapid use of glucose stores and life-threatening glucose deficiency and hypoglycemia. They often are missed because feeding can temporarily correct the glucose deficiency.[41] Persistent hyperinsulinism is caused by insulinomas and genetic defects in the potassium channels of

the pancreatic β-cells. The latter lead to persistent depolarization of the β-cell membrane, activation of voltage-dependent calcium channels, calcium entry into the β-cells, and activation of insulin secretion. Such defects often are refractory to glucose replacement.[42]

Once identified, infants with recurrent hypoglycemia should be treated with IV glucose to values >2.0 but <4.5 mmol/L (>45 but <80 mg/dL) until stable and receive full IV nutrition while they are advanced on enteral feeding. Lactose is the preferred sugar in enteral feedings, as it contains galactose, which does not stimulate insulin secretion and is rapidly cleared by the liver to promote glycogen formation for later use between feedings. Plasma insulin concentrations should be obtained when glucose concentrations are very low. Hydrocortisone can be added after 24–48 hours, but only for temporary treatment for 1–2 days. Diazoxide helps in most cases, as can Somatostatin (long-acting Octreotide Acetate, which inhibits insulin and growth hormone release) when Diazozide does not. Glucose concentrations should be followed closely, frequent feedings given, and long fasting periods avoided. More severe cases require imaging studies and pancreatic insulin secretion tests to determine persistent K^+ channel disorders (most are genetic) and the need for partial or total pancreatectomy. These disorders can be severe, and most result in neurological injury. Neonates with recurrent hypoglycemia should not go home without a diagnosis and without proving that the infant can maintain normal glucose concentrations over several fast-feed cycles for 2–3 days if the hypoglycemia was severe and difficult to treat.

Summary of definition of hypoglycemia and relevance to clinical practice

Neonatal hypoglycemia represents an imbalance between glucose supply and utilization and may result from a multitude of disturbed regulatory mechanisms. A rational definition of neonatal hypoglycemia must account for the fact that acute clinical signs and long term neurological sequelae of neonatal hypoglycemia occur with a continuum of low plasma glucose values of varied duration and severity. The permanent neurological impact of a given plasma glucose concentration in a given infant is dependent on multiple factors, some of which cannot even be measured. The definition of the blood glucose concentration at which intervention is indicated must be tailored to the clinical situation and the particular characteristics of a given infant. No systematic studies have been done to demonstrate the risks or benefits of using a specific blood glucose concentration as a threshold for intervention in neonatal hypoglycemia for any group of infants. Therefore, using any specific blood glucose concentration to define neonatal hypoglycemia for all infants is without rigorous scientific justification.

Recognizing this limitation, Rozance and Hay recently conducted a review of the neonatal hypoglycemia literature in an attempt to determine which low glucose concentrations, their duration, and their association with clinical signs might indicate potential long term neurological injury (Table 2).[43] Unfortunately, the effect of any diagnostic and/or treatment approach or any set of guidelines to manage glucose metabolism and concentrations in neonates on preventing long term complications of “hypoglycemia” (however defined) has never been tested by a sufficiently large, randomized, controlled trial. Key to preventing complications from glucose deficiency, therefore, is to focus less on numerical values of glucose concentration, identify infants at risk, promote early and frequent feedings, normalize glucose homeostasis, measure glucose concentrations early and frequently in infants at risk, and treat promptly when glucose deficiency is marked and symptomatic.

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Table 1

Conditions indicating risk of neonatal hypoglycemia[18]

Maternal conditions
Presence of diabetes or abnormal result to glucose tolerance test
Preeclampsia and pregnancy-induced or essential hypertension
Previous macrosomic infants
Substance abuse
Treatment with beta-agonist tocolytics
Treatment with oral hypoglycemic agents
Late antepartum to intrapartum administration of IV glucose
Neonatal conditions
Preterm birth
Intrauterine growth restriction
Perinatal hypoxia-ischemia
Sepsis
Hypothermia
Polycythemia-hyperviscosity
Erythroblastosis fetalis
Iatrogenic administration of insulin
Congenital cardiac malformations
Persistent hyperinsulinemia
Endocrine disorders
Inborn errors of metabolism
Late antepartum to intrapartum administration of IV glucose
Poor feeding, especially after feeding well

Table 2

Conditions that should be present before considering that long term neurological impairment might be related to neonatal hypoglycemia.[43]

1	Blood or plasma glucose concentrations below 1 mmol/L (18 mg/dL). Such values definitely are abnormal, although if transient there is no study in the literature confirming that they lead to permanent neurological injury.
2	Persistence of such severely low glucose concentrations for prolonged periods (hours, probably >2–3 hrs, rather than minutes, although there is no study in human neonates that defines this period).
3	Early mild-moderate clinical signs (primarily those of increased adrenalin [epinephrine] activity), such as alternating CNS signs of jitteriness/tremulousness vs. stupor/lethargy or even a brief convulsion, that diminish or disappear with effective treatment that promptly restores the glucose concentration to the statistically normal range (>2.5 mmol/L or 45 mg/dL).
4	More serious clinical signs that are prolonged (many hours or longer), including coma, seizures, respiratory depression and/or apnea with cyanosis, hypotonia or limpness, high-pitched cry, hypothermia, and poor feeding after initially feeding well. These are more refractory to short term treatment.
5	Concurrence of associated conditions, particularly persistent excessive insulin secretion and hyperinsulinemia with repeated episodes of acute, severe hypoglycemia with seizures and/or coma (although sub-clinical, often severe, hypoglycemic episodes occur in these conditions and might be just as injurious).