Glucose Homeostasis and the Neonatal Brain: A Sweet Relationship

Stephanie Amendoeira, RN(EC), MN, NP-Pediatrics, NNP-Dip
Carol McNair, RN(EC), MN, PhD(c), NNP-BC, NP-Pediatrics
Jennie Saini, RN(EC), MN, NP-Pediatrics, NNP-Dip
Sharifa Habib, RN(EC), MN, NP-Pediatrics, NNP-Dip

Continuing Nursing Education (CNE) Credit

The test questions are provided in this issue. The posttest and evaluation must be completed online. Details to complete the course are provided online at academyonline.org. Sign into your ANN account or register for a non-member account if you are not a member. A total of 1.5 contact hour(s) can be earned as CNE credit for reading this article, studying the content, and completing the online posttest and evaluation. To be successful, the learner must obtain a grade of at least 80 percent on the test. The test expires three (3) years from the publication date of this journal.

Disclosures: The authors, members of the activity planning committee, and the test panel have no relevant financial interests or affiliations with any commercial interests related to the subjects discussed within this article. No commercial support or sponsorship was provided for this educational activity. Neither ANN nor ANCC endorses any commercial products discussed/displayed in conjunction with this educational activity.

The Academy of Neonatal Nursing is accredited with distinction as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Provider, Academy of Neonatal Nursing, approved by the California Board of Registered Nursing, Provider #CEP 6261; and Florida Board of Nursing, Provider #FBN 3218, CE Broker #50-3066.

The purpose of this article is to discuss the physiology of glucose homeostasis, the pathophysiology of neonatal hypoglycemic brain injury, prevention of injury, and some of the long-term outcomes seen as a result of hypoglycemia in the neonate

Funding. The author(s) received no specific grant or financial support for the research, authorship, and/or publication of this article.

Accepted for publication
February 5, 2020

Abstract

Glucose is the primary substrate for energy metabolism in the brain and although the brain is dependent on a constant glucose supply for normal function, both local energy stores and the supply of alternate substrates are limited. In utero, the placenta provides a continuous supply of glucose to the fetus while transition to extrauterine life marks an abrupt change in substrate delivery and a major change in glucose metabolism where insufficiencies and disruptions can occur. Hypoglycemia is one of the most common biochemical disturbances in the neonatal period, affecting a wide range of neonates. Prolonged or persistent low plasma glucose concentrations can lead to neonatal brain injury and abnormal neurological outcomes. This article discusses fetal and neonatal metabolic adaptation, the physiology of glucose homeostasis, hypoglycemic brain injury (HBI), and neurodevelopmental long-term outcomes.

Keywords: euglycemia; HBI; hypoglycemia; metabolic; neonatal hypoglycemic brain injury (HBI)

Hypoglycemia is one of the most common biochemical disturbances seen in the neonatal period and a common cause of brain injury as glucose is the brain's primary metabolic fuel.[1] The transfer from fetal glucose to neonatal glycogenesis is complex, although healthy full-term neonates are generally equipped to manage the transition.[1] However, many factors make neonates susceptible to more significant hypoglycemia. Following birth there is an expected drop in glucose levels as the neonate adapts to extrauterine life; however, any persistent or recurrent hypoglycemia may have significant impact on the neonatal brain.[2]

Persistent hypoglycemia is hypoglycemia that lasts beyond the first 24 to 48 hours of life.[2–4] Although all neonates are theoretically at risk for hypoglycemia, preterm, late-preterm, large for gestational age (LGA), small for gestational age (SGA), those with intrauterine growth restriction (IUGR), infants of diabetic mothers (IDM), and neonates with perinatal stress are all at increased risk for persistent hypoglycemia.[2] The level and duration of hypoglycemia associated with neurologic sequelae is not well established.[5] However, neonatal hypoglycemia (NH) can result in a catastrophic brain injury.[5,6] This article describes the physiology of glucose homeostasis, the pathophysiology of neonatal hypoglycemic brain injury (HBI), and long-term outcomes.

PHYSIOLOGY OF GLUCOSE HOMEOSTASIS

Insulin and glucagon are the primary hormones that regulate glucose metabolism. Glucose must cross the plasma membrane to be utilized by cells in the body and this

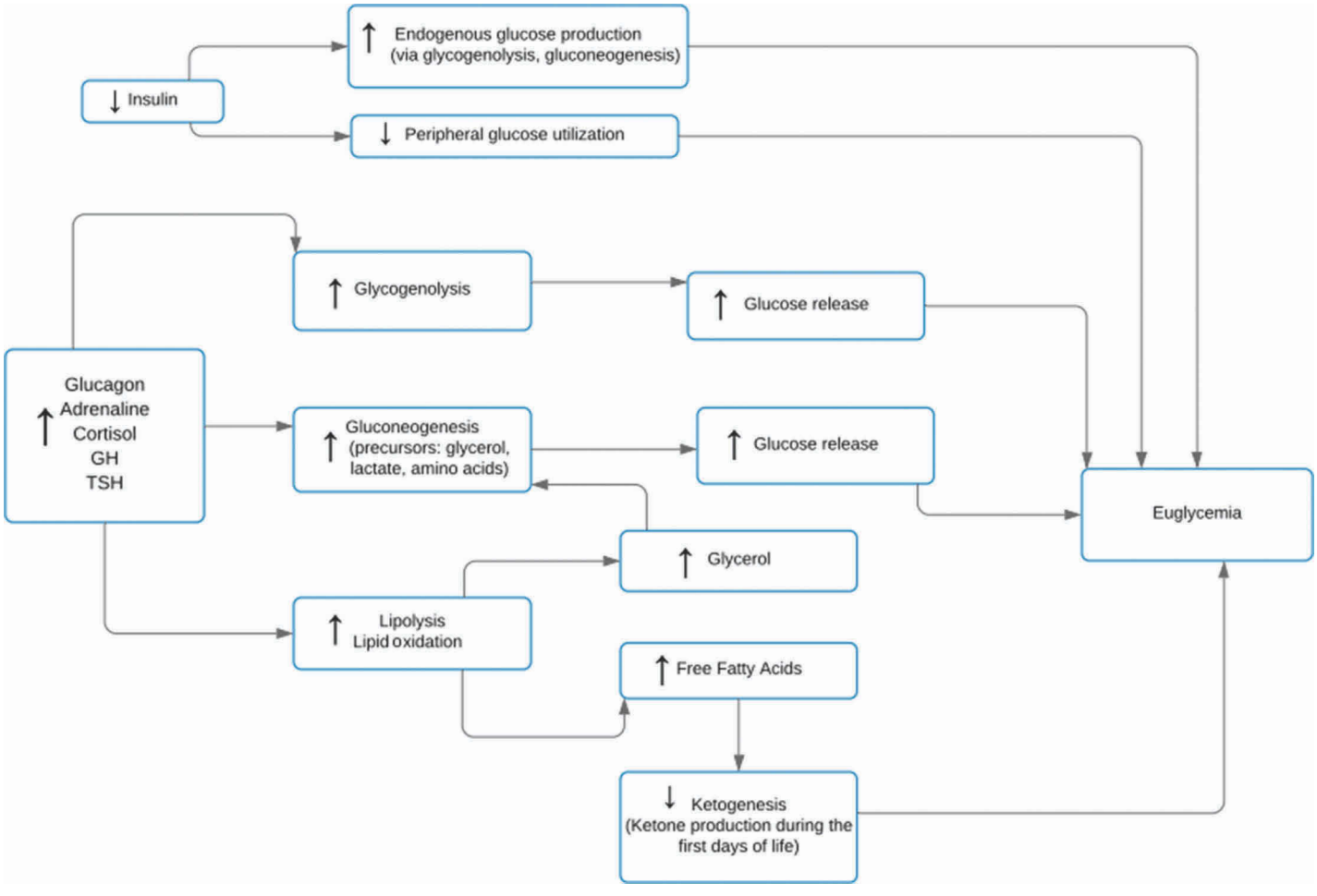
http://dx.doi.org/10.1891/0730-0832.39.3.137

is highly influenced by the hormone, insulin.[7] Through the process of facilitated diffusion, insulin enables glucose to enter the cell by changing the cell wall permeability; however, this process occurs differently in the brain, in that cerebral utilization of glucose is not dependent on insulin.[7] Cerebral glucose transport through the blood–brain barrier is regulated by a carrier-mediated, facilitated diffusion that involves glucose transporters, a process that is dependent on plasma glucose concentrations.[7]

Glucose is the primary substrate for energy metabolism necessary for all organ function during the perinatal, neonatal, and postnatal periods. A considerable portion of the placental transfer of glucose is used by the fetal brain.[8] Prior to birth, the fetus depends entirely on the continuous maternal supply and the carrier-meditated placental transfer of glucose for energy because there is very little endogenous glucose production during fetal life.[9] Although enzyme systems necessary for glucose production develop early in fetal life, endogenous fetal glucose production only occurs under extreme and abnormal circumstances.[8] While the fetus does not produce glucose readily, fetal insulin production is present at 10–12 weeks' gestation.[9] As the fetus approaches term gestation glucose and other substrates are stored as glycogen and fat in anticipation of birth.[10] The high insulin to glucagon ratio in the fetal circulation results in the activation of glycogen synthesis and suppression of glycogenolysis (formation of glucose from glycogen).[11] Most fetal glycogen is produced in the third trimester and deposited in the skeletal muscle and liver.[10] In addition to glycogen, the fetus also stores fat in adipose tissue where most triglyceride synthesis occurs in the third trimester.[10] The marked increase in glycogen and triglyceride synthesis during this period is associated with an increase in circulating insulin and cortisol that is necessary for the maturation and activation of the metabolic pathways required following birth.[11]

Transition from fetal to neonatal life is very complex with physiologic challenges that require metabolic adaptation to maintain appropriate plasma glucose concentrations.[9] Following birth, with the clamping of the umbilical cord, the continuous transplacental glucose supply and nutrient

FIGURE 1 ■ The physiological changes to maintain glucose levels in healthy term neonates.



Source: Adapted from Güemes M, Rahman SA, Hussain K. What is a normal blood glucose? *Arch Dis Child.* 2016;101:569–574.

delivery abruptly ceases and neonatal endogenous glucose metabolism, including insulin regulation, begins.[11] In the healthy term neonate, several metabolic, hormonal, and physiologic changes occur that facilitate the extrauterine adaptation necessary to maintain glucose homeostasis; these are outlined in Figure 1. Plasma glucose concentrations undergo a transitional phase with a normal physiologic nadir in the first few hours of life and this stimulates endogenous glucose production in the healthy, term neonate.[12] Healthy newborn infants will adapt to intermittent feeding, digestion, and intestinal absorption of nutrients that stimulate production of hormones and trigger a cascade of changes in their gastrointestinal function and metabolic adaptation to extrauterine life.[9] Conversely, in premature or SGA infants this complex process of hormonal and metabolic adaptation is immature and underdeveloped.[9]

In the immediate newborn period, there is a rapid surge in plasma catecholamine concentrations, such as epinephrine, an increase in cortisol and glucagon levels, and a parallel decrease in circulating plasma insulin levels.[12] Simultaneously, the physiologic decline in plasma glucose concentration triggers glycogen phosphorylase enzyme activity that stimulates an increase in hepatic glucose release through glycogenolysis contributing to the regulation of glucose homeostasis in the first few hours of life (Table 1).[10] It is estimated that healthy, term infants have only enough glycogen to maintain a glucose supply for about ten hours, during which time glycogenolysis can rapidly lead to the depletion of glycogen stores.[11] Therefore, other mechanisms are required to maintain glucose homeostasis. The increase in glucagon, reversing the relatively low fetal glucagon-to-insulin ratio, induces the synthesis of phosphoenolpyruvate carboxykinase (PEPCK), an enzyme required for hepatic gluconeogenesis, where a healthy, term infant is capable of significant gluconeogenesis by four to six hours of life.[10,11] The surge in plasma catecholamine concentrations and the exhaustion of glycogen stores promotes the activation of lipolysis, releasing free fatty acids (FFA) that can be metabolized to provide precursors, such as glycerol and amino acids, for gluconeogenesis as well as providing energy in the form of adenosine triphosphate (ATP).[10,11,13] These fatty acids are also catabolized to produce ketone bodies that are used as an alternate fuel by most tissues, including the brain.[13] The release of epinephrine, a catecholamine, by the adrenal glands permits additional release of glucose from the liver; however, with prolonged low plasma glucose concentrations, growth hormone and cortisol are also released to mobilize fat and protein substrates as alternate energy sources that can be utilized for cerebral function.[13] These adaptive changes occur to replace the glucose supply previously received via the placenta.[10]

TABLE 1 ■ Counterregulatory Pathways Involved in Maintaining Glucose Homeostasis

Glycogenolysis	• Hepatic glycogen converted to glucose • Stimulated by ↑epinephrine, glucagon, ↓ insulin
Gluconeogenesis	• Glucose from noncarbohydrate sources, e.g., lactic acids, amino acids, glycerol
Lipolysis	• Formation of free fatty acids and glycerol • Glycerol is converted to glucose
Ketogenesis	• Free fatty acids converted to ketones

Neonatal glucose homeostasis provides the brain and other vital organs with enough glucose supply for energy metabolism. Normal glucose concentrations are maintained by factors that control glucose production and glucose utilization.[9] Until an exogenous supply of glucose is provided, either by enteral feedings or administration of intravenous fluids, endogenous hepatic glucose production serves as the most significant source of glucose to meet a neonate's metabolic requirements.[11] When rates of glycogenolysis and gluconeogenesis do not equal the rate of glucose utilization due to a disruption in the hormonal control mechanisms or variability of substrate supply, disturbances of glucose homeostasis occur, most commonly resulting in neonatal hypoglycemia.

DEFINING NEONATAL HYPOGLYCEMIA

The definition of neonatal hypoglycemia is still controversial as no one single value can define hypoglycemia for individual neonates.[1,14,15] The American Academy of Pediatrics (AAP) defines hypoglycemia as blood glucose <40 mg/dL (2.2 mmol/L), but suggests maintaining a glucose level >45 mg/dL (2.5 mmol/L) if symptomatic.[16] The Pediatric Endocrine Society (PES) defines it as blood glucose <50 mg/dL (2.8 mmol/L) in neonates without concern for a congenital hypoglycemia disorder.[3] PES has a more conservative definition, noting that the AAP definition is based on an observational study of preterm infants who had asymptomatic hypoglycemia multiple times during hospitalization, and at 18-month follow-up were found to have impaired neurodevelopment.[12] It is, however, important to note that in a follow-up study of this same cohort at age 15, there was no persistent difference in neurodevelopmental status.[12] The normal glucose range is dependent on various factors such as the neonate's size, gestational age, underlying conditions, and available energy sources.[1,12] Whole blood glucose levels are noted to be 10–18 percent less than plasma glucose levels, and it is important to consider the source utilized in these thresholds and in clinical practice.[1] One study of healthy breastfed infants found the lowest plasma glucose levels occurred during the first 24 hours of life and could be as low as 25 mg/dL (1.4 mmol/L) to 32 mg/dL (1.8 mmol/L) without sequalae.[17] Approximately 12–14 percent of normal, appropriate for gestational age (AGA), breastfed neonates will have a plasma glucose <47 mg/dL (2.6 mmol/L) in the first 72 hours of age.[18] The AAP focuses on recommendations in the first 24 hours of life, while PES suggests that after the first 48 hours of life the threshold for intervention should be even higher, 60 mg/dL (3.3 mmol/L).[12] It is unlikely that a consensus will be reached on a numerical definition of hypoglycemia, given that specific responses to hypoglycemia

occur within a range and can be determined by the presence of alternative energy sources.[1,3]

The current hypoglycemia threshold, most clinicians agree, is 36–47 mg/dL (2–2.6 mmol/L),[1] but in healthy term neonates, plasma glucose levels can range from 25 to 110 mg/dL (1.4–6.1 mmol/L) within the first few hours but should be a least 60–100 mg/dL (3.3–5.6 mmol/L) after 72 hours of age.[14] However, for high-risk neonates, poorer outcomes have been reported with plasma glucose levels <47 mg/dL (2.6 mmol/L).[13] In one study, published by McKinlay and associates in 2015, neonates >35 weeks' gestation, who had interventions to maintain plasma glucoses >47 mg/dL (2.6 mmol/L) had no evidence of neuronal injury at two years of age.[19]

Symptomatic hypoglycemia may be readily detected by the clinician, although clinical signs may overlap with other etiologies. Symptomatic, hypoglycemic infants present with jitteriness or tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic events or tachypnea, weak or high-pitched cry, limpness or lethargy, difficulty in feeding, and eye rolling.[1,13] In asymptomatic neonates who are not identified to be at risk and screened, hypoglycemia may go undetected for a prolonged period, placing them at increased risk for the long-term sequelae.

ETIOLOGY OF HYPOGLYCEMIA

A significant number of neonates with hypoglycemia do not exhibit symptoms. If asymptomatic, the only way to identify hypoglycemic neonates is through screening glucose assessments. The challenge here lies in knowing which neonate has a transient normal low glucose versus a neonate who will have repeated or prolonged hypoglycemia. It is postulated that prolonged or repeated hypoglycemia predisposes neonates to brain injury, but there is no clear consensus.[1,2,4,14] Identifying at-risk populations may be useful in implementing additional surveillance and monitoring in an attempt to quickly identify and mitigate hypoglycemia (Table 2).

TABLE 2 ■ Risk Factors for Abnormal Glucose Homeostasis

Prematurity
IUGR
SGA
LGA
IDM
Perinatal stress
Inborn errors of metabolism
Genetic disorders
Maternal beta-blocker use

Abbreviations: IDM = infant of diabetic mother; IUGR = intrauterine growth restriction; LGA = large for gestational age; SGA = small for gestational age.

Genetic conditions such as Beckwith–Wiedemann syndrome, Turner syndrome, Costello syndrome, congenital hypopituitarism, congenital adrenal hyperplasia, and trisomy 21, to name a few, are known to be associated with hypoglycemia in the neonatal period. These infants warrant increased screening.[1,12,20] Metabolic and endocrine disorders such as those that affect amino acid, galactose, fructose, carnitine, and fatty acid metabolism as well as glycogen synthesis disorders, ketone synthesis and utilization defects, and defects in glucose transport can all lead to hypoglycemia.[1,12,21] In cases where hypoglycemia persists, it is important to consider these causes of impaired glucose regulation.

While genetic risk factors for neonatal hypoglycemia cannot be forgotten, it is pertinent to further examine the more proximate causes of hypoglycemia in the neonate, such as SGA, IUGR, prematurity, LGA, or IDM. These risk factors, along with additional postnatal variables, are outlined in Table 2. The etiology of hypoglycemia in these populations arises from a variety of factors such as inadequate substrate availability, growth restriction, hyperinsulinemia, and inadequate enzyme production.

Inadequate Substrate

A discussion of hypoglycemia would be incomplete without addressing inadequate carbohydrate intake as a cause of hypoglycemia. Whether because of the lack of adequate milk, from which fatty acids and sugars are used as metabolic fuels,[22] or an inability of the neonate to adequately transfer milk from the source, perhaps because of neurological or congenital abnormalities, insufficient glucose intake can lead to hypoglycemia. In a healthy term infant, the liver should contain up to three times the concentration of glycogen of an adult liver, providing a ready energy source to sustain the neonate through periods of reduced glucose availability.[1] When glucose availability fails to meet the metabolic requirements, glycogenolysis and gluconeogenesis must be activated to ensure a constant supply of fuel. A failure to sufficiently activate these processes, or limited substrate availability, can lead to hypoglycemia.

Growth Restriction

The definition of SGA is variable and may include infants who measure less than the tenth or third percentile for gestational age, or more than two standard deviations below the mean for their gestational age. These infants may be constitutionally small given their genetic makeup or ethnicity and may not necessarily be small because of pathological reasons. However, a significant portion of SGA infants, by one estimate up to 70 percent, experience hypoglycemia.[21] IUGR infants, conversely, may not be SGA by definition, but are those infants who have not met their optimal growth potential because of genetic factors or in utero environmental factors.[12] Both of these groups of infants, as well as those infants born prematurely, are at increased risk for hypoglycemia because of inadequate glycogen and substrate

for gluconeogenesis.[12,21] Interestingly, up to a third of SGA infants will have hyperinsulinemic hypoglycemia, thought to be related to altered insulin secretion as a result of intrauterine stress and catecholamine production.[23,24] Fetal adaptations in insulin secretion result from high catecholamine levels during placental insufficiency.[24]

Lack of glycogen stores, FFAs, or precursors to gluconeogenesis such as muscle mass may occur in premature, late premature, SGA, or IUGR infants related to their lack of intrauterine time to accrue the necessary adipose and glycogen stores or because of growth restriction caused by a variety of maternal and placental factors. In the preterm infant, the usual deposition of glycogen and accrual of fat in the third trimester has been interrupted and thus limits the available stores.[1] The insufficiency of substrate results in an inability to maintain glucose homeostasis through the mechanisms of glycogenolysis and gluconeogenesis.

Hyperinsulinemia

While a fetus cannot produce its own glucose and relies on constant maternal–placental delivery, glucose levels can be regulated because insulin production is present from early gestation.[1,8,9] In the setting of poorly-controlled maternal diabetes, the fetus will increase insulin secretion and will present with growth above that expected as a result of this surplus in anabolic steroid.[1] After birth this hyperinsulinemia may persist, but without the excessive maternal glucose supply, leads to overutilization of glucose and results in hypoglycemia.[21,22]

Hyperinsulinism is the most common cause for the inability to maintain euglycemia.[22] Findings suggestive of hyperinsulinemia are outlined in Table 3. Hyperinsulinism should be suspected as the underlying cause of neonatal hypoglycemia when it is coupled with higher than expected glucose requirements (>8 mg/kg/minute in the term infant) or in infants noted to be macrosomic. The classic macrosomic appearance, with normal for age head circumference but large body mass for gestational age, suggests hyperinsulinism of fetal origin. This occurs in uncontrolled maternal gestational diabetes and should be differentiated from infants who are constitutionally large.[22] While there may be some debate on the true definition of macrosomia, it is conventionally accepted that any term infant weighing more than 4 kg, with excessive body fat and increased glycogen storage in the liver, kidney, skeletal muscle, and heart, typically noted by clinicians as organomegaly, is macrosomic.[25,26] Of note, while excessive glucose has long been thought to be the main cause of macrosomia in these neonates, maternal hyperlipidemia and increased transfer of lipids to the fetus also accounts for the excessive weight gain.[25]

TABLE 3 ■ Findings Suggestive of Hyperinsulinism

Persistent hypoglycemia
Severe hypoglycemia
Symptomatic hypoglycemia
Increased glucose requirements (above expected) to maintain normal serum glucose (>8–10 mg/kg/min)
Elevated C-peptide or proinsulin levels

Large for gestational age status is recognized as a risk factor for hypoglycemia. These infants may or may not be IDMs. LGA infants are those having a mean weight above the 90th percentile, or those with a mean weight two standard deviations above that expected for their gestational age.[25,26] While their LGA status may, in part, be related to their genetic makeup or ethnicity, as in the SGA population, it cannot be overlooked that these LGA infants may, in fact, be IDMs who were not identified prenatally.[25] In macrosomic newborns born to women without a diagnosis of diabetes, C-peptide levels in cord blood have been found to be elevated, suggesting increased insulin levels in this population.[12,27] Studies in gestational diabetes readily identify the challenges of diagnosis, including that globally there exist differences in doses for oral glucose challenges, which may impact the ability to diagnose gestational diabetes and capture outcome data.[27,28] It is also possible that LGA infants' mothers may have episodic hyperglycemia, which actually confers increased risk of macrosomia, with surges in maternal glucose promoting fetal insulin secretion.[25]

Hyperinsulinism may be short lived, or can be sustained for weeks. In the SGA population, hyperinsulinism may be more prolonged and require pharmocotherapy, beyond the scope of this article, while transient hyperinsulinemia may resolve within a few days.[1] If hyperinsulinism persists, there should be consideration given to the possibility of congenital hyperinsulinism, which is a rare genetic disorder leading to unregulated or inappropriate insulin production. Findings that should be investigated for hyperinsulinism can be found in Table 3.

Inadequate Enzyme Production

The premature or extremely low birth weight infant and IUGR infants have the additional risk of hypoglycemia not only because of inadequate substrate but also due to reduced availability of enzymes necessary for gluconeogenesis such as PEPCK, glucose-6-phophatase, fructose-1,6-diphosphatase, and pyruvate carboxylase.[21,22] Without the necessary levels of enzymes, gluconeogenesis is limited, and results in an inability to maintain euglycemia via this mechanism. As mentioned earlier, infants with hyperinsulinemia (LGA, IDM) may also produce insufficient amounts of PEPCK as well as other counterregulatory hormones necessary for glycogenolysis, lipolysis, and ketogenesis, further limiting this at-risk neonate's ability to restore normal glucose levels.[22,25,29]

Perinatal Stress

Perinatal stress is well recognized as a risk factor for hypoglycemia. Stressors may include birth asphyxia, ischemia,

or fetal distress.[30] Significant hypoxic injury in the perinatal period can impact liver function and potentially limit enzyme activity necessary for gluconeogenesis, leading to hypoglycemia in this vulnerable population.[22] Following perinatal asphyxia there may be transiently increased metabolic demands that lead to increased glucose production via glycogenolysis, but sustained hypoxia leads to anaerobic metabolism and quick depletion of glycogen stores.[1] Additionally, perinatal stress is also known to be a risk factor for hyperinsulinemia that can persist for several weeks after birth.[1,30] As previously mentioned, perinatal stress can set off a cascade with long-lasting effects: surges of catecholamines in fetal life, leading to suppression of insulin, eventually translating to altered cell functioning and excessive insulin production in postnatal life.[24] It is important to note that up to 25 percent of IDMs may experience perinatal asphyxia that can be, in part, related to their large size and increased risk of birth-related trauma, such as shoulder dystocia.[25]

HYPOGLYCEMIC BRAIN INJURY

Newborn infants encounter several challenges when attempting to establish euglycemia in the immediate postnatal period. Newborns are capable of short-term glycogenolysis, which cleaves glucose, but this metabolic pathway is contingent upon existing glycogen stores. Newborns must wait at least four to six hours after birth for the onset of gluconeogenesis, and this is contingent upon adequate postnatal intake of substrate and the accumulation of necessary enzymes. A failed or delayed metabolic transition to extrauterine life may leave neuronal cells devoid of necessary glucose or energy intake. This increases the risk for postnatal HBI.

In the immature neonatal brain, neuronal ATP levels and neurological function are maintained during transient hypoglycemia.[30] Neonatal hepatic glucose production does not sufficiently supply the neonatal brain with energy during prolonged hypoglycemia; therefore, the mobilization of deposited fat is important for energy metabolism.[8] The use of these alternative substrates, such as ketone bodies and lactate, for cerebral energy contributes to the maintenance of neonatal glucose homeostasis.[8] Although these metabolic pathways are functional in providing alternate fuel sources to maintain plasma glucose concentrations during the neonatal period, several inefficiencies exist. Insufficient ketone production, lower amount of FFAs, and limited glycogen stores overall reduce the amount of glucose available for utilization.[12] When plasma glucose concentrations are reduced, cerebral blood flow increases as a primary compensatory mechanism; however, neuronal cells cannot extract sufficient glucose for their metabolic needs from the low plasma glucose concentrations despite the increase in cerebral blood flow.[30,31] Transfer of glucose across the blood–brain barrier is also dependent on plasma glucose concentrations and the activity of carrier-mediated, glucose transporters on the vascular endothelium and cell membranes.[11] The level of glucose transporters is decreased in the neonate when compared to the older infant, which can also limit cerebral glucose uptake.[11,30,31] Therefore, when physiological disruptions occur leading to inadequate defenses against prolonged periods of hypoglycemia, the effects on the brain can be devastating and neonates can develop permanent brain injury.

With the inadequate supply of glucose to the brain during prolonged hypoglycemia there can be a subsequent decrease in cerebral electrical activity, cell membrane breakdown, and altered amino acid metabolism including the production of glutamate.[11] Glutamate is an excitatory amino acid neurotransmitter in the central nervous system that is thought to play a major role in the pathogenesis of HBI.[11] Hypoglycemia is associated with an increased release of glutamate and in the neonatal period, the receptors for glutamate, in particular the N-methyl-D aspartate (NDMA)–type receptor, are well developed and more commonly seen in the immature brain; these receptors are associated with ion channels that transport sodium and calcium into the cell and potassium out of the cell.[11] Excessive activation of NDMA receptor activity increases the cell concentrations of sodium and calcium to levels that impair inhibitory mechanisms to maintain neuronal homeostasis thereby altering the cell membrane ion gradients.[11] During hypoglycemia, energy-dependent mechanisms for restoring normal sodium and calcium ion gradients cannot function due to the depletion of ATP and an excess of calcium ions can activate a cascade of intracellular activities including activating cell proteases and lipases, altering mitochondrial function, triggering free-radical formation, and changing neurotransmitter synaptic function, which can result in neuronal damage and necrosis.[11,31,32] Changes to mitochondrial metabolism and function play a significant role in HBI.[11,32] There is a reduction in mitochondrial oxygen and increased oxygen free-radicals, which causes damage to the mitochondrial membranes and DNA.[11,32] Mitochondrial DNA fragmentation interferes with the ability of the cell to restore ATP levels; local depletion of high-energy substrates can alter calcium ion levels within and outside the mitochondrial membrane, inducing apoptosis and leading to neuronal necrosis.[11,32] The ability to utilize alternative energy substrates and the maintenance of cerebral perfusion are important factors in determining the differences observed in the patterns of brain injury seen in neonatal hypoglycemia versus neonatal hypoxia.[30] When hypoxia occurs, cardiac function is compromised and cardiac output is reduced. A reduction in cardiac output in conjunction with the impaired autoregulation of cerebral blood flow that can accompany hypoxia leads to ischemia and results in a lack of oxygen and glucose delivery to the brain. This type of injury occurs more often in the watershed area and is dominated by gray and white matter changes.[30,32] Hypoglycemia seems to potentiate the effects of hypoxia.[30] Neonatal HBI occurs when local energy stores and the supply of alternate substrates are depleted; neurotransmitter synaptic functions are disrupted causing dysregulation and massive excretion of excitotoxins inducing cytotoxic edema

and neuronal cell death in the parietal–occipital and thalamic brain regions.[11,31,32] It remains unclear as to why these specific brain regions are the most vulnerable and affected by neonatal hypoglycemia.

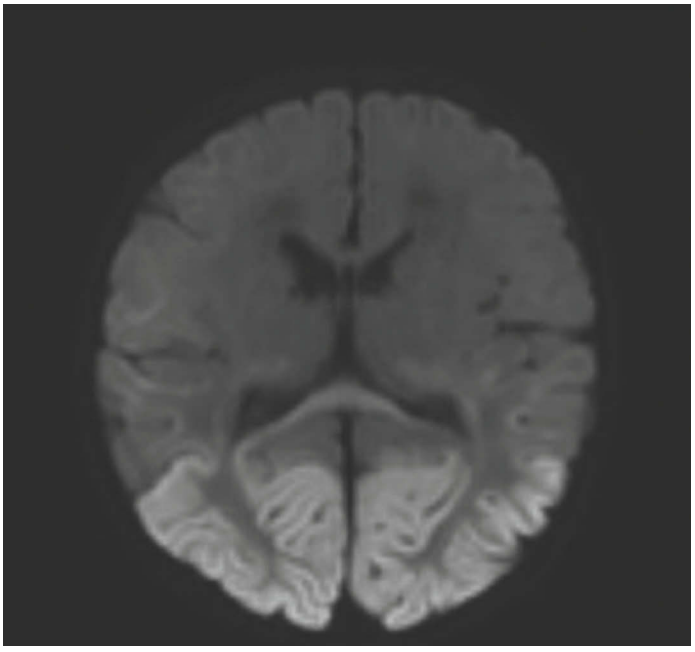
MRI CHANGES SEEN IN HBI

Symptomatic neonatal hypoglycemia can result in brain injury detected by magnetic resonance imaging (MRI); however, the degree or duration of NH associated with brain injury on MRI is unknown.[4] The first case report in 1994 by Spar and colleagues noting neuroradiologic changes commented on findings of cerebral cortex thinning in the occipital lobes with some basal ganglia involvement as well.[33] Subsequent to this, there have been several studies confirming the findings of parietooccipital white matter abnormalities, as well as abnormal findings in the deep gray matter structures of the basal ganglia and thalamus.[5]

Published in 2008, Burns and colleagues conducted a retrospective cohort study of 35 term neonates with symptomatic NH and no evidence of hypoxic–ischemic encephalopathy; these neonates (>36 weeks' gestation) had at least one episode of hypoglycemia ≤47 mg/dL (2.6 mmol/L) and underwent brain MRI in the first six weeks of life. Sixty-three percent of the patient population had transient hypoglycemia that resolved promptly after treatment; the remainder had prolonged or recurrent NH. Patterns of brain injury secondary to NH are more varied than previously described as per the study results.[34] Ninety-four percent of infants had some level of evidence of white matter changes, with 80 percent categorized as moderate or severe.[34] Most infants had global white matter abnormalities (39 percent), with only 29 percent having severe injury localized to the parietooccipital cortex and subcortical white matter with 18 percent of infants only having posterior changes.[34] Basal ganglia and thalamus involvement were noted in 40 percent of infants.[34] The severity of NH did not correlate to the pattern of brain injury. There were also no distinguishing MRI changes for transient versus prolonged or recurrent NH. Of note, the presence of seizures over several days was associated with moderate to severe white matter injury. Children who did not have seizures had no cortical involvement, although normal to moderately abnormal white matter changes were noted.[34] A subset of children with transient seizures on Day 1 of life had normal to severe changes on MRI scans.[34] Clinical implications of these MRI findings do not present until later in life.

Diffusion-weighted imaging (DWI) is an MRI technique with which increased diffusion restriction can be seen in cytotoxic or myelin edema. DWI has been utilized to assess diffusion restriction on MRI scans of infants with NH in a retrospective cohort study of 45 patients by Tam and colleagues.[5] Neonates with documented glucose values of 47 mg/dL (2.6 mmol/L) who underwent MRI during their admission were included in the study. Diffusion restriction in bilateral occipital poles had been detected in term neonates who underwent DWI within six days after NH onset; any DWI studies conducted after one week of NH would not result in the expected diffusion restriction pattern of injury because the cytotoxic or myelin edema would have resolved.[5] Neonatal hypoglycemia resulted in varying degrees and distribution of occipital lobe injury (Figure 2). Preterm neonates with neonatal hypoglycemia did not show diffusion restriction. It could be hypothesized this is because of a lesser degree of myelination in the preterm brain, variable metabolic activity in the preterm brain, or variance in metabolic activity of the glial cells in term neonates, more specifically in the occipital white matter.[5]

FIGURE 2 ■ MRI image of HBI.



MRI diffusion-weight imaging (DWI) after neonatal hypoglycemia. Diffusion restriction in a neonate born at a gestational age of 38 weeks, evaluated with DWI four days after hypoglycemia onset. Showing diffusion restriction in the bilateral cortex of occipital lobes, corpus callosum, and mesial part of occipital lobe with involvement of right-sided optic radiation—typical finding of neonatal HBI.

Neonatal hypoglycemia is also common in term infants with neonatal hypoxic-ischemic encephalopathy (HIE) and there have been various studies detailing the MRI patterns of brain injury in HIE. However, when neonatal hypoglycemia and neonatal encephalopathy or HIE coexist, an MRI pattern of posterior white matter and posterior nuclei of the thalamus injury has been documented.[6]

NEURODEVELOPMENTAL OUTCOMES

There is limited evidence, generally of low quality, to predict the impact of neonatal hypoglycemia on neurodevelopment and many studies are contradictory. A systematic review by Boluyt and colleagues on neurodevelopment after neonatal hypoglycemia found 18 eligible studies: 16 of poor

quality with only 2 considered high quality.[35] There was note of significantly decreased motor and mental scores as well as significantly increased incidence of cerebral palsy or global developmental delay at 18 months comparing preterm neonates with neonatal hypoglycemia versus normoglycemic control preterm neonates.[35] To the contrary, Goode and colleagues, who performed a secondary analysis on data from the Infant Health and Development program (785 infants ≤37 weeks' gestation and ≤2,500 g with glucose levels recorded), divided the patients into four categories based on glucose values (ranging from ≤35 mg/dL [≤1.9 mmol/L], 36–40 mg/dL [2.0–2.2 mmol/L], 41–45 mg/dL [2.3–2.5 mmol/L] and 46–180 mg/dL [2.55–10 mmol/L]) and noted no significant intellectual or academic difference in preterm infants with or without neonatal hypoglycemia.[36]

There is a traditional association of neonatal hypoglycemia with occipital lobe injury. Tam and colleagues reported 55 percent poor or absent cortical responses on visual evoked potentials (VEPs) in a population of 20 term neonates.[5] Neonates with diffusion restriction noted in the occipital lobe were more likely to have abnormal VEPs and cortical–visual deficits. Visual deficits ranged between squint, field defects, and cortical–visual and visual–spatial impairments.[5] The study authors recommended that family counseling on the potential of future visual abnormalities be provided for infants with neonatal hypoglycemia and associated DWI changes in the occipital lobes on MRI.[5]

Burns and colleagues reported that presentation of neonatal hypoglycemia with seizures in the neonatal period was associated with poor long-term neurologic outcomes. Thirty-five percent of neonates developed seizures later, but before the age of two years, these ranging from infantile spasms to focal or generalized seizures.[34] Hypoglycemia–occipital syndrome has been described in a retrospective study of 27 patients with neonatal hypoglycemia (excluding for confounding factors like HIE, electrolyte abnormalities, infection or other factors such as trauma).[37] The authors describe a triad of neonatal hypoglycemia, visual disturbance, and epilepsy (predominantly occipital lobe epilepsy) as the main findings in neonates and children with a history of neonatal hypoglycemia.[37]

Reassuringly, studies have noted correlation between MRI findings and long-term outcomes.[19,34,38,39] Burns and colleagues reported 80 percent of neonates (n = 35) with moderate to severely impaired outcomes were noted to have severe white matter changes on MRI.[34] Neonates with mild white matter changes were noted to have a normal to mildly impaired outcome. Neonates with severe white matter changes who went on to develop mild to moderately impaired outcomes had unilateral white matter injury, which supports the assumption that the contralateral hemisphere has some ability to compensate.[34]

McKinlay and colleagues performed a prospective cohort study involving 528 neonates >35 weeks' gestation considered to be at risk for hypoglycemia.[38] The neonates were treated to maintain glucose values >47 mg/dL (2.6 mmol/L). Fifty-three percent of neonates in the study had neonatal hypoglycemia.[38] When treated, neonatal hypoglycemia was not associated with an increased risk of impairment or processing difficulties at two years of age in neonates with hypoglycemia versus normoglycemic controls.[38] This finding was consistent even among children with multiple or severe episodes of neonatal hypoglycemia.[19] The same group of researchers followed the same infants at 4.5 years of age and noted a two to three-fold greater risk of lower executive function (working memory, flexibility and attention, delay inhibition, and complex or conflict inhibition) and lower visual–motor integration scores in infants with neonatal hypoglycemia compared to normoglycemic controls.[38] Executive function impairment has been associated with attention deficit or hyperactivity disorder, learning difficulties, and conduct disorders. Additionally, visual–motor integration impairment has been associated with poor math, writing, and reading performance.[38]

Similarly, a recent systematic review of 12 low-quality studies found no difference in the risk for neurodevelopmental impairment in early childhood (two to five years of age).[39] This review did find an association with increased risk of visual–motor impairment in this age range in two studies, also deemed as low-quality evidence.[39] No difference in the development of epilepsy was noted with exposure to neonatal hypoglycemia.[39] Study results were different in the 6–11 years age range with an increased risk for low language and literacy scores as well as low numeracy scores.[39] Consequently, studies assessing neonatal hypoglycemia and the impact on neurodevelopment must have longer term endpoints for follow-up assessment. General developmental tests completed in follow-up at infancy are not likely to capture or demonstrate the impact of neonatal hypoglycemia on the development of the brain.

Hypoglycemia is one of the most common metabolic disorders during the neonatal period. As discussed, persistent or recurrent hypoglycemia can cause some degree of neonatal brain injury including cognitive impairment, visual disturbances, seizures, and other sequalae; however, quantifying the risk has remained challenging with ongoing discrepancies and varying agreements among practitioners on how to best manage these infants. Neonatal HBI is not well known or understood by some practitioners and there are limited diagnostic criteria available, because of the lack of clinical manifestations, to identify signs of HBI. MRI studies, however, have become increasingly important as a diagnostic and prognostic tool. An improvement in understanding the outcomes of HBI could inform decisions on when practitioners should intervene and how quickly, to correct the hypoglycemia.

CONCLUSION

Hypoglycemia management is challenging and screening infants at the correct times is of utmost importance. The

management of hypoglycemia for healthy term neonates or at-risk neonates can be guided by the clinical practice guidelines available from the AAP, Canadian Paediatric Society, Pediatric Endocrine Society, or other reputable sources in your region of practice.[3,13,40] Understanding the underlying pathophysiology of neonatal hypoglycemia in at-risk populations, including SGA, LGA, IDM, and premature infants, can aid the clinician in identifying neonates at risk who are then appropriately screened, managed, and followed in the first week of life to ensure glucose homeostasis is maintained. Persistent or recurrent hypoglycemia can lead to permanent brain injury that may include visual disturbances, hearing impairment, cognitive abnormalities, secondary epilepsy, and other long-term neurologic sequelae that can be prevented.[32] Each unit should develop or follow preexisting evidence-based guidelines or policies that guide health care providers in managing neonatal hypoglycemia based on the population they serve. Obstetrical units, postpartum units, and NICUs all have a role to play in prevention of HBI.[40]

REFERENCES

1. Chandran S, Rajadurai VS, Abdul Haium AA, Hussain K. Current perspectives on neonatal hypoglycemia, its management, and cerebral injury risk. *Res Rep Neonatal.* 2015;5:17–30. https://doi.org/10.2147/RRN.S55353
2. Rozance PJ, Hay WW. New approaches to management of neonatal hypoglycemia. *Matern Health Neonatol Perinatol.* 2016;2:3. https://doi.org/10.1186/s40748-016-0031-z.
3. Thorton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for the evaluation and management of persistent hypoglycemia in neonates, infants and children. *J Pediatr.* 2015;167:238–245. https://doi.org/10.1016/j.jpeds.2015.03.057
4. Rozance PJ. Pathogenesis, screening, and diagnosis of neonatal hypoglycemia. UpToDate. Wolters Kluwer. https://www.uptodate.com/contents/pathogenesis-screening-and-diagnosis-of-neonatal-hypoglycemia/print. Accessed October 10, 2019.
5. Tam EWY, Widjaja E, Blaser SI, Macgregor DL, Satodia P, Moore AM. Occiptal lobe injury and cortical visual outcomes after neonatal hypoglycemia. *Pediatrics.* 2008;122:507–512. https://doi.org/10.1542/peds.2007-2002
6. Wong DST, Poskitt KJ, Chau V, et al. Brain injury patterns in hypoglycemia in neonatal encephalopathy. *Am J Neuroradiol.* 2013;34:1456–1461. https://doi.org/10.3174/ajnr.A3423
7. Milcic TL, Nash P. Neonatal glucose homeostasis. *Neonatal Netw.* 2008;27:203–207. https://doi.org/10.1891/0730-0832.27.3.203
8. Gustafsson J. Neonatal energy substrate production. *Indian J Med Res.* 2009;130:618–623.
9. Güemes M, Rahman SA, Hussain K. What is a normal blood glucose? *Arch Dis Child.* 2016;101:569–574. https://doi.org/10.1136/archdischild-2015-308336
10. Merenstein GB, Gardner SL. *Handbook of Neonatal Intensive Care.* 6th ed. St. Louis, MO: Elsevier; 2006:368–390.
11. McGowan JE. Neonatal hypoglycemia. *Pediatr Rev.* 1999;20:e6–e15. https://doi.org/10.1542/pir.20-7-e6
12. Mitanchez D. Glucose regulation in preterm newborn infants. *Horm Res.* 2007;68:265–271. https://doi.org/10.1159/000104174
13. Thompson-Branch A, Havranek T. Neonatal hypoglycemia. *Pediatr Rev.* 2017;38:147–157. https://doi.org/10.1542/pir.2016-0063
14. Aziz K, Dancy P, Canadian Paediatric Society, Fetus and newborn committee. Screening guidelines for newborn at risk for low blood glucose. *Paediatr Child Health.* 2004;9:723–729. https://doi.org/10.1093/pch/9.10.723
15. Rozance PJ, Wolfsdorf JI. Hypoglycemia in the newborn. *Pediatr Clin N Am.* 2019;66:333–342. https://doi.org/10.1016/j.pcl.2018.12.004
16. Adamkin D, Committee on Fetus and Newborn. Clinical report—Posnatal glucose homeostasis in late-preterm and term infants. *Pediatrics.* 2011;127:575–579. https://doi.org/10.1542/peds.2010-3851
17. Hoseth E, Joergensen A, Ebbesen F, Moeller M. Blood glucose levels in a population of healthy breast fed, term infants of appropriate size for gestational age. *Arch Dis Child Fetal Neonatal Ed.* 2000;83:F117–F119. https://doi.org/10.1136/fn.83.2.F117
18. Nicholl R. What is the normal range of blood glucose concentrations in healthy term newborns? *Arch Dis Child.* 2003;88:238–239. https://doi.org/10.1136/adc.88.3.238
19. McKinlay CJD, Alsweller JM, Ansell JM, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. *N Engl J Med.* 2015;373:1507–1518. https://doi.org/10.1056/NEJMoa1504909
20. Adamkin DH. Neonatal hypoglycemia. *Semin Fetal Neonat Med.* 2017;22:36–41. https://doi.org/10.1016/j.siny.2016.08.007
21. Sharma A, Davis A, Shekhawat PS. Hypoglycemia in the preterm neonate: Etiopahtogenesis, diagnosis, management and long-term outcomes. *Transl Pediatr.* 2017;17:335–348. https://doi.org/10.21037/tp.2017.10.06
22. Hawdon JM. *Homeostasis of Carbohydrate and Other Fuels. Avery's Neonatology.* 7th ed. Philadelpha, PA: Wolters Kluwer; 2016.
23. Kumar J, Singh A. A brief review of hyperinsulinism in small for gestational age infants. *J Med Sci Clin Res.* 2017;5:15379–15383. https://doi.org/10.18535/jmscr/v5i1.29
24. Limesand SW, Rozance PJ. Fetal adapatations in insulin secretion result from high catecholamines during placental insufficiency. *J Physiol.* 2017;595:5103–5113. https://doi.org/10.1113/JP273324
25. Hay WW. Care of the infant of the diabetic mother. *Curr Diab Rep.* 2012;12:4–15. https://doi.org/10.1007/s11892-011-0243-6
26. Lawrence EJ. A matter of size: Part 2. Evaluating the large-for-gestational age neonate. *Adv Neonat Care.* 2007;7:187–197. https://doi.org/10.1097/01.ANC.0000286335.06047.28
27. Schaefer-Graf UM, Rossi R, Bührer C, et al. Rate and risk factors of hypoglycemia in large-for-gestational-age newborn infants of nondiabetic mothers. *Am J Obstet Gynecol.* 2002;187:913–917. https://doi.org/10.1067/mob.2002.126962
28. Cho HY, Jung I, Kim SJ. The association between maternal hyperglycemia and perinatal outcomes in gestational diabetes mellitus patients: A retrospective cohort study. *Medicine.* 2016;95:e4712. https://doi.org/10.1097/MD.0000000000004712
29. de Rooy L, Hawdon J. Nutritional factors that affect the postnatal metabolic adaptation of full-term small- and large-for-gestational-age infants. *Pediatrics.* 2002;109:E42. https://doi.org/10.1542/peds.109.3.e42
30. Barkovich AJ, Ali FA, Rowley HA, Bass N. Imaging patterns of neonatal hypoglycemia. *Am J Neuroradiol.* 1998;19:523–528.
31. Hosagasi NH, Aydin M. A perspective on neurological aspects of neonatal hypoglycemia. *Int J Neurol Res.* 2016;2:269–276. https://doi.org/10.17554/j.issn.2313-5611.2016.02.52
32. Su J, Wang L. Research advances in neonatal hypoglycemic brain injury. *Transl Pediatr.* 2012;1:108–115. https://doi.org/10.3978/j.issn.2224-4336.2012.04.06
33. Spar JA, Lewine JD, Orrison WW. Neonatal hypoglycemia: CT and MR findings. *Am J Neuroradiol.* 1994;15:1477–1478.

34. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics*. 2008;122:65–74. https://doi.org/10.1542/peds.2007-2822
35. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: A systematic review and design of an optimal future study. *Pediatrics*. 2006;117:2231–2243. https://doi.org/10.1542/peds.2005-1919
36. Goode RH, Rettiganti M, Li J, et al. Developmental outcomes of preterm infants with neonatal hypoglycemia. *Pediatrics*. 2016;138:e20161424. https://doi.org/10.1542/peds.2016-1424
37. Karimzadheh P, Tabarestani S, Ghofrani M. Hypoglycemia-occipital syndrome: A specific neurologic syndrome following neonatal hypoglycemia. *J Child Neurol*. 2011;26:152–159. https://doi.org/10.1177/0883073810376245
38. McKinlay CJD, Alsweller JM, Anstice NS, et al. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. *JAMA Pediatr*. 2017;171:972–983. https://doi.org/10.1001/jamapediatrics.2017.1579
39. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: A systematic reveiw and meta-analysis. *Neonatalogy*. 2019;115:116–126. https://doi.org/10.1159/000492859
40. Gregory KE. New approaches to care of the infant with hypoglycemia. *J Perinat Neonatal Nurs*. 2016;34:284–287. https://doi.org/10.1097/JPN.0000000000000213

About the Authors

Stephanie Amendoeira, RN(EC), MN, NP-Pediatrics, NNP-Dip, is a neonatal nurse practitioner who works in a quaternary-level NICU in Toronto.

Carol McNair, RN(EC), MN, PhD(c), NP-Pediatrics, NNP-BC, is a neonatal nurse practitioner who works in a quaternary-level NICU in Toronto and a PhD student at the University of Toronto.

Jennie Saini, RN(EC), MN, NP-Pediatrics, NNP-Dip, is a neonatal nurse practitioner who works in a quaternary-level NICU in Toronto.

Sharifa Habib, RN(EC), MN, NP-Pediatrics, NNP-Dip, is a neonatal nurse practitioner who works in a quaternary-level NICU in Toronto.

For further information, please contact:
Stephanie Amendoeira, RN(EC), MN, NP-Pediatrics, NNP-Dip
SickKids, Neonatology
555 University Ave
Toronto, Ontario, M5G1X8
E-mail: stephanie.amendoeira@sickkids.ca