Glucose Metabolism in the Late Preterm Infant

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“The questions that arise at the bedside are, (1) How low a glucose concentration is too low? (2) Which glucose concentration causes brain damage? (3) How long should it be low before we encounter irreversible brain damage”

Prematurity and low birth weight are important determinants of neonatal morbidity and mortality. A rising trend of preterm births is caused by an increase in the birth rate of near-term infants [1]. Near-term infants are defined as infants of 34 to 36 6/7 weeks gestation. The term “near-term” recently was renamed as the “late preterm” to alert health care providers to anticipate increased potential problems that may present in labor and delivery, in the nursery, and beyond [2–4]. Demands on limited acute care beds in neonatal ICUs, along with established clinical practices, often result in early transition of these infants to the well baby nursery and to the mother’s room to honor the rooming in practice. This transition takes place once spontaneous respirations and adequate oxygenation are established. This is exacerbated further by early discharge of the mother and baby resulting in increased rehospitalizations. Treating these infants as term well babies serves as a distinct disadvantage to this subgroup. Transitional problems persist and consist of poor thermoregulation, inability to adequately establish feeding, unrecognized hypoglycemia, and subsequent issues with hyperbilirubinemia. It is dangerous to assume that the incidence of hypoglycemia in the late preterm infant is similar to the infant born at full term. Postnatal decrease in plasma glucose concentration in preterm infants is much greater

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than in term infants, suggesting poor postnatal adaptation [5]. The incidence of hypoglycemia in preterm infants is three times greater than in full-term newborn infants, and nearly two-thirds of these infants require intravenous dextrose infusions [4]. Further, the compensatory mechanisms responsible for protecting the brain from hypoglycemic injury are not entirely in place, posing a greater risk to this subpopulation of late preterm infants. Association of hypoglycemia with neurodevelopmental abnormalities has prompted increased recognition, anticipation, diagnosis, and therapy of neonatal hypoglycemia [6–9]. Severe hypoglycemia is recognized to cause neuronal cell death and subsequent adverse neurodevelopment [7,10]; however, the level at which hypoglycemia becomes clinically important, warranting intervention, is not well-defined [11,12]. Although current methods for assessing effects of hypoglycemia are imperfect, the injury to central nervous system depends on the degree of prematurity, presence of intrauterine growth restriction (IUGR), intrauterine compromise, genotype, blood flow, metabolic rate, and availability of other substrates. Therefore, early recognition of glucose metabolic abnormalities pertaining to late preterm infants is essential to provide appropriate and timely interventions in the newborn nursery. Although many of the investigations have targeted full-term infants, premature infants inclusive of the extremely low birth weight infants and the intrauterine growth-restricted infants, adequately powered studies restricted to only the late preterm infants are required and need future consideration.

Incidence

At birth, the glucose concentration is approximately 80% of maternal glucose, but it falls to its lowest nadir between 30 and 90 minutes after birth and stabilizes between 40 to 100 mg/dL. During this transition in the first 2 to 4 hours of life, 8% of babies develop hypoglycemia that requires intervention. How many of these babies belong to the late preterm subpopulation is unknown. The incidence of scheduled cesarean section versus cesarean section following labor or vaginal delivery contributing toward the development of hypoglycemia has not been investigated specifically. The presence of labor may prove to be essential for some of the hormonal and enzymatic adaptations that are necessary to preserve circulating glucose concentrations.

Pathophysiology

Fetus

Eighty percent of the fetal energy consumption is provided by glucose. The fetus is solely dependent on maternal glucose that is supplied transplacentally by a process of facilitative diffusion. This passive diffusion process is mediated primarily by a saturable, stereo-specific, carrier-mediated system consisting of
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a family of closely related membrane-spanning glycoproteins termed the facilitative glucose transporters (GLUT1). Isoform GLUT1 (Michaelis-Menten constant aka Michaelis constant or Km 1 to 2 mmol) is the predominant transporter in the human placenta, with the isoform GLUT3 (Km 0.8 mM) found during early gestation and in fetal vasculature [13]. These two isoforms provide the basis for transplacental transport of glucose. The fetal glucose concentration generally is maintained at two thirds that of the mother to provide the gradient necessary for passive transport of glucose from mother to fetus. Under normal conditions, the fetus is incapable of producing endogenous glucose. Under conditions of limited transplacental glucose supply, however, the fetus has the ability to produce glucose by glycogenolysis and gluconeogenesis.

Transition at birth

Once the cord is clamped, the newborn has to adapt swiftly to a life of independence and learn to produce endogenous glucose to meet the energy (ATP) demands of cellular oxidation. During this transition, the newborn infant’s circulating glucose concentration decreases to one third of the maternal concentration (40 to 60 mg/dL) by 2 to 4 hours of age. In the late premature infant, this concentration may be lower at 30 to 40 mg/dL [11,12,14]. The maintenance of euglycemia depends on postnatal induction of hepatic glycogenolysis and gluconeogenesis in response to postnatal changes in plasma catecholamines, glucagon, insulin, and corticosteroids that are conducive to glucose production. The increase in plasma concentrations of catecholamines (epinephrine, norepinephrine and dopamine) is preserved in preterm and late preterm newborns with an accentuated epinephrine response compared with term newborns [15]. This change is accompanied by a decline in circulating insulin concentrations and a subsequent surge in glucagon concentrations. Glucose-regulated insulin secretion by the pancreatic β–islets is immature, resulting in unregulated insulin production during hypoglycemia [16]. Nevertheless, disturbances in glucose homeostasis are common, because metabolic reserves including glycogen are low in late preterm infants, similar to IUGR infants. The risk of hypoglycemia increases further when energy demands increase because of coexisting conditions of sepsis, birth asphyxia, or cold stress [11,17,18]. The blood glucose level stabilizes at a normal value of 60 to 80 mg/dL within 12 to 24 hours after birth. The neonatal glucose requirement is 6 to 8 mg/kg/min as measured by stable isotope tracer technology, a value higher than that observed in adults (3 mg/kg/min) [19]. Hepatic glucose production by glycogenolysis and gluconeogenesis is essential for maintaining euglycemia. Other gluconeogenic substrates, consisting of increased concentrations of circulating glycerol and fatty acids, are encountered because of the dramatic postnatal increase in fat oxidation secondary to catecholamine-induced lipolysis [5,20]. Available amino acids also are converted to glucose. Further, other substrates such as ketones and lactate are used as alternate fuels by the
brain in the presence of hypoglycemia. Late preterm and IUGR infants face the challenge of maintaining euglycemia secondary to developmentally immature hepatic enzyme systems (eg, PEPCK) for gluconeogenesis [21] and lower accumulation of hepatic glycogen reserves that are depleted quickly after birth. The immaturity of the gluconeogenic enzymatic pathways was determined when the administration of alanine failed to improve gluconeogenesis in preterm infants [22].

Definition

Although it is recognized that low circulating glucose concentrations have detrimental effects, the actual level at which such effects occur remains unknown, making it difficult to come up with a clinically useful definition of hypoglycemia. During earlier times, statistical definitions were relied upon for clinical decision making, based on values that represented two standard deviations below the mean glucose value of a given population. This definition determined the incidence in a particular population, but it did not define hypoglycemia adequately. A physiological definition subsequently was rendered at less than 45 mg/dL based on abnormal electroencephalographic or increased latency of auditory brainstem-evoked responses (ABR) [23]. The latter observation was made in 10 out of 11 children with a blood glucose of less than 47 mg/dL [24]. At a glucose concentration less than 18 mg/dL, the electroencephalogram (EEG) was isoelectric, demonstrating the critical nature of such low values. More recently, 340 term newborn infants were examined, and higher numbers of rhythmic EEG patterns of less than 10s with asymmetry were observed in infants who had hypoglycemia [25]. Examination of 20 term newborn infants compared with 20 controls revealed frontal sharp transients in hypoglycemic infants with bilateral asynchrony along with coarser theta waves and the appearance of delta waves [26]. Further in the low birth weight infants, persistent hypoglycemia for 5 days was associated with a poor neurological outcome [27]. Although this physiological definition may herald immediate neurological dysfunction in term babies, the impact of these EEG and ABR changes on long-term outcome is unknown. Meta analysis of different investigations suggested that plasma glucose of less than 25 mg/dL for several hours increased the relative risk for adverse neurological outcome with a 21% (confidence interval [CI] from 14% to 27%) incidence of significant neurological sequelae [28]. This study, however, did not rule out adverse neurological outcomes at other glucose values. Hence the search for a functional definition that impacts long term neurological outcome in the late preterm infants is ongoing. More importantly, a quest for a cut-off value continues toward developing bedside management guidelines for these infants. Although the definitions of asymptomatic versus symptomatic hypoglycemia have assisted toward the need for immediate intervention, given that some of the symptoms are nonspecific,
the recognition of symptomatic hypoglycemia may not be that easy. Signs and symptoms of hypoglycemia include:

- Changes in level of consciousness: irritability, excessive crying, lethargy, or stupor
- Apnea episodes, cyanosis
- Feeding poorly
- Tachypnea, tachycardia, grunting
- Hypothermia
- Hypotonia-limpness
- Tremor-seizures, jitteriness

Even if the health care team is astute at detecting hypoglycemia-related symptoms that usually are caused by either counter-regulation or the absence of alternate substrates to fuel brain oxidative metabolism, the cause for lack of symptoms remains evasive. The asymptomatic state may relate to a lack of the compensatory counter-regulatory hormonal response similar to the unawareness state described in older children, which may be ominous, or the presence of adequate alternate substrates protecting the brain’s energy requirement. Most investigations in asymptomatic hypoglycemic term infants have revealed a neurologically intact outcome, supporting the latter [29]. Similar studies do not exist specifically in the subpopulation of late preterm infants.

The more challenging task is to come up with a cut-off circulating glucose threshold value that dictates intervention in the late preterm infant. The reason this is difficult is because circulating glucose concentrations are merely the tip of an iceberg, reflecting the net effect of glucose production, use, and clearance. Although glucose concentrations less than 45 mg/dL are acceptable during the transition phase of life, glucose concentrations less than 50 to 60 mg/dL following the transition are considered abnormal. The ideal parameter to assess is not the glucose concentration but rather the glucose delivery to tissues. This is calculated by the Fick’s principle: (a-v) glucose concentration × cardiac output. This demonstrates that tissue glucose delivery depends, not only on the arterio–venous difference in circulating glucose concentration, but also on the cardiac output/tissue blood flow. Thus, the glucose concentration that predetermines a detrimental effect may vary depending on the cardiac output, being higher in situations of hypotension and shock and lower when normotensive. Thus the threshold varies depending on the clinical presentation. This concept is helpful and can be derived when caring for ill neonates, but most often one needs to decipher the significance of a glucose value obtained by a bedside screening test followed by a laboratory assessed value. The American Academy of Pediatrics guidelines suggest glucose screening to be undertaken at the bedside. This is now routine in most nurseries, and the bedside test should be reliable yet easy to perform on a large scale. In addition, the site of sampling, the hematocrit of blood at the time of sampling, presence of alcohol or heparin in a collected sample, and the timeliness of performing the test after blood collection all influence the ultimate result.
“Prolonged hypoglycemia should be avoided by close bedside monitoring of vulnerable infants whilst avoiding excessively invasive management in populations of neonates, which may jeopardize the successful establishment of breast feeding” [30].

This statement applies to late preterm infants, because establishment of breast feeding is a challenge in this subpopulation setting them up for hypoglycemia. Because most of the bedside monitoring devices involve a blood draw and are fraught with inaccuracies (ranging from 10% to 15%), a need for developing a noninvasive continuous glucose monitoring sensor exists. To this end, 96 measurements were performed in 16 very low birth weight infants at 23 to 30 weeks who were 584 to 1387 g in body weight [31]. Researchers used disposable glucose oxidase-based platinum electrode sensor that catalyzes interstitial glucose oxidation, generating an electrical current every 10 seconds using a Minimed sensor (Medtronic, Northridge, California) that can last for 7 days of monitoring. The R² obtained was 0.87, with $P < .001$ at less than 10 mM. The glucose values obtained from Minimed at <10 mM glucose concentration were 0.06 mM lower than the values obtained by the Yellow Springs Instrument (Yellow Springs, Ohio; YSI) and correlated significantly ($r^2 = 0.87, P < .001$). However at >10 mM glucose concentration the difference was −0.106 mM when compared to the YSI laboratory measurements with a lower correlation ($r^2 = 0.69$ at $P < .001$).

Hyperinsulinism

It is important to address the state of hyperinsulinism that frequently is encountered in infants of diabetic mothers and those born to obese insulin-resistant mothers. Given the incredible increase in overweight and obese individuals in the United States, the incidence of gestational diabetes is increasing, resulting in macrosomic infants [32,33]. These infants usually are delivered by cesarean section because of cephalo–pelvic disproportion or shoulder dystocia. Thus these infants run the risk of becoming late preterm infants with hyperinsulinism (Box 1). In the presence of uteroplacental insufficiency, these infants may be growth restricted yet appropriate for gestational age. These infants are at high risk for developing hypoglycemia that may require aggressive intervention. In addition, persistent hyperinsulinemic hypoglycemia of infancy (PHHI) syndromes also can present in the late preterm infant, requiring aggressive and timely intervention to prevent neurological impairment [34,35]. It is clear from animal and human studies that the hyperinsulinemic hypoglycemia is worse than the low glycogen reserve-related hypoglycemia of the late preterm infant. Thus if a late preterm infant presents with a PHHI syndrome, the neurological outcome is worse. This is related to extremely low ketone concentrations secondary to the high insulin concentrations [36]. Thus, the alternate substrate also is lacking, making the brain highly vulnerable to injury. In the infant of a diabetic mother, the increase in free iron in brain incites oxidant injury to the detriment of the infant [37,38].
Box 1. Causes of hypoglycemia in the late preterm infant

**Transient hypoglycemia in the late preterm infant**

Maternal conditions
- Glucose infusion in the mother
- Preeclampsia
- Drugs: tocolytic therapy, sympathomimetics
- Infant of diabetic mother

Neonatal conditions
- Prematurity
- Respiratory distress syndrome
- Twin gestation
- Neonatal sepsis
- Perinatal hypoxia-ischemia
- Temperature instability: hypothermia
- Polycythemia
- Specific glucose transporter deficiency
- Isoimmune thrombocytopenia, Rh incompatibility

**Persistent hypoglycemia in the late preterm infant**

Hyperinsulinism
- Nesidioblastosis, beta cell hyperplasia, sulfonylurea receptor defect
- Beckwith-Wiedemann syndrome
- Infant of diabetic mother

Endocrine disorders
- Pituitary insufficiency
- Cortisol deficiency
- Congenital glucagon deficiency

Inborn errors of metabolism
- Carbohydrate metabolism: glycogen storage disease, galactosemia, fructose-1-6-diphosphatase deficiency
- Amino acid metabolism: maple syrup urine disease, propionic acidemia, methylmalonic acidemia hereditary tyrosinemia
- Fatty acid metabolism: acyl-coenzyme dehydrogenase defect, defects in carnitine metabolism, beta-oxidation defects

Defective glucose transport
Protective mechanisms in brain

The higher glucose requirement in neonates reflects the glucose uptake by brain, which accounts for \( \sim 80\% \) of total glucose produced. Glucose is transported across the blood–brain barrier into neurons and glia (astrocytes) by two major glucose transporter isoforms, GLUT1 found mainly in the blood–brain barrier and astrocytes and GLUT3 in neurons. The astrocytes are the local power houses of glycogen stores serving as an immediate source of glucose. In addition to glucose, other substrates, particularly ketones and lactate, are transported across the blood–brain barrier and into astrocytes by the monocarboxylate transporter (MCT) isoform 1 and into neurons by MCT2 [39]. The lactate shuttle, recently described as an alternate protective mechanism in the presence of hypoglycemia, consists of lactate being produced in astrocytes that then is transported as fuel to meet the energy requirements of neurons in the presence of limited glucose supply [40,41]. Whether the astrocytic glycogen stores are replete in the late preterm infant remains unknown. What is known is that alternate fuels such as lactate, pyruvate, amino acids, free fatty acids, ketone bodies, and glycerol are used by the brain during hypoglycemia. Unlike term infants, however, late preterm infants and IUGR infants are incapable of mounting an adequate mature peripheral counter-regulatory ketogenic response [5] to hypoglycemia. This is because of inadequate lipolysis in these infants who do not have the necessary adipose tissue stores and fail to demonstrate adequate milk intake. In lieu of these protective responses, these infants are vulnerable to adverse long-term neurodevelopmental outcome [27,42,43]. Another built-in protective mechanism is that cerebral glucose use is low at birth (18 \( \mu \text{mol/min/100 g} \)), increasing to 60 \( \mu \text{mol/min/100 g} \) only at 50 weeks postconceptional age, which reflects the value at six years of age [44]. The late preterm infant is also able to increase brain blood flow by recruiting underperfused capillaries in response to hypoglycemia as determined by near infrared spectroscopy (NIRS) [45]. Despite this response, the lack of an adequate ketogenic response with limited glycogen reserves that build up only in late gestation enhances vulnerability to neurological injury [46]. This is of particular importance, because the cerebral extraction coefficient for ketone bodies is highest only when expressed as a fraction of cerebral coefficient for oxygen, which is low in the newborn [30,47].

Clinical neurological presentation

Perinatal hypoxia–ischemia may decrease availability of ketone bodies further; therefore hypoglycemia after hypoxic–ischemic events may cause further damage in late preterm or IUGR infants. Initial hypoglycemia with severe fetal acidemia was observed to cause brain injury in term infants. Retrospective examination of 185 term infants with an umbilical
arterial pH of less than 7.00 and an initial blood glucose within 30 minutes of birth [48] demonstrated that 27 (14.5%) infants had an initial blood glucose of less than 40 mg/dL. Fifteen (56%) of these 27 infants with a blood glucose of less than 40 mg/dL versus 26 (16%) of the 158 infants with a blood glucose of greater than 40 mg/dL had an abnormal neurological outcome. Although no difference in the requirement for cardiopulmonary resuscitation or a 5-minute Apgar score of less than 5 was observed between the groups, an increased incidence of abnormal fetal heart rate tracing and meconium staining in hypoglycemic infants was noted. This study suggests that asphyxial injury is associated with a higher incidence of hypoglycemia and sets the stage for subsequent development of neurodevelopmental compromise.

Another multi-center trial that was not targeted at hypoglycemia specifically identified 668 infants with hypoglycemia (blood glucose of less than 40 mg/dL); 433 infants had moderate hypoglycemia, and 104 infants presented with persistent hypoglycemia between 3 and 30 days of life. When hypoglycemia was recorded on 5 or more separate days, the adjusted mental and motor developmental scores at 18 months (corrected age) were reduced by 13 to 14 points, and the incidence of developmental delay was increased by a factor of 3.5 [49]. A longer follow-up study involving 85 small for gestational age (SGA) preterm neonates determined the incidence of hypoglycemia to be 73%. Infants with repeated episodes of hypoglycemia presented with a reduced head circumference and lower scores on psychometric testing at 3.5 and 5 years of age [27]. A retrospective study of children with occipital epilepsy at 12 years of age demonstrated that all these children were hypoglycemic at birth and developed epilepsy as early as 5 months of age [50]. Eighteen infants (six infants who were SGA, two infants of diabetic mothers, and 10 normal infants born between 36 and 42 weeks gestational age) were examined in a separate study. These infants had at least one episode of hypoglycemia (less than 45 mg/dL) after 6 hours of age to exclude transient hypoglycemia, and were symptomatic. Symptoms included tremors, apathy, tachypnea, irritability, hypotonia, and feeding difficulties, which all disappeared when treated. The control group consisted of 10 healthy infants with no hypoglycemia. Ultrasound and MRI at birth, and at 2 months of age, were performed. Thirty nine percent of abnormalities, consisting of patchy hyperintense lesions in the occipital periventricular white matter and thalamus, were observed. These injuries may be related to processes of axonal migration and synaptogenesis that occur in the occipital region during the neonatal period. On developmental follow-up, most of the abnormalities recovered to baseline at 2 months of age; however, no longer-term follow-up was reported [51]. Another small cohort of 8-year-old children born to diabetic mothers and who suffered neonatal hypoglycemia presented with neurological dysfunction related to the attention deficit disorder, including hyperactivity, impulsiveness, and easy distractibility, in addition to deficits in motor control and perception [52].
**Detection of brain injury**

Although EEG changes have been defined, proton spectroscopy has determined the presence of increased lactate during hypoglycemia [53]. In contrast, phosphorus spectroscopy can detect decreased ATP levels when alternate fuels are exhausted [53]. Ultrasound changes have not been found to be sensitive enough, and CT has limited usefulness. MRI, however, particularly the diffusion-weighted T1 and T2 images, has revealed occipital white matter and thalamus changes caused by acute insult, while chronic changes have presented as periventricular leukomalacia. Positron emission tomography has been useful in determining 2-deoxyglucose and lactate uptake by the brain in infants. More recently, investigations have focused on functional MRI in an attempt to pinpoint the affliction in response to visual and auditory stimuli and in response to specific tasks.

**Neuronal injury**

Neonatal hypoglycemia can cause seizures, permanent neuronal injury, and death. Hypoglycemia is associated with gray and white matter injuries in the immature brain, and the specific mechanisms responsible for hypoglycemic brain injury have formed the subject of many investigations. Many animal studies have demonstrated that longer periods of hypoglycemia are required than that of hypoxic–ischemia to produce the same degree of brain injury [54]. Hypoglycemia superimposed on hypoxic–ischemia causes more severe injury [55]. Hypoglycemia leads to excitotoxicity with accumulating aspartate and glutamate in brain [53]. The superficial cerebral cortex, the dentate gyrus, hippocampus, and caudate nucleus are vulnerable areas to hypoglycemic injury [10].

The neonatal brain, and especially the cerebral white matter, have relatively low oxygen consumption. Therefore glucose supply is essential to meet the metabolic demands [56]. The major source of brain glucose to meet the metabolic requirements is from an adequate blood flow in addition to plasma glucose concentration (a-v glucose concentration × brain blood flow). Hypoglycemic conditions result in a compensatory increase in cerebral blood flow, and this response is shown to be preserved in preterm infants [6,45,57]. When hypoglycemia is prolonged and the alternate substrate use is exhausted, biochemical effects of brain metabolism develop (Fig. 1). The activities of glutamate receptor/channel complexes are enhanced in the immature brain to promote activity-dependent plasticity. Excitotoxicity is an important mechanism involved in perinatal brain injury. Excitatory synaptic transmission in the mammalian brain is mediated primarily by means of α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) and N-methyl-D-aspartate (NMDA)-type receptors [58] (Fig. 2). Glutamate is the major excitatory neurotransmitter, and most neurons, oligodendrocytes, and astrocytes possess receptors for glutamate. Perinatal insults such as hypoxia–ischemia,
Fig. 1. Intracellular consequences of hypoglycemia.

Fig. 2. Brain neurochemical changes in response to hypoglycemia.
stroke, hypoglycemia, and kernicterus, can disrupt synaptic function, leading to accumulation of extracellular glutamate and excessive stimulation of these receptors [10]. Excessive stimulation of glutamate receptor/ion channel complexes trigger calcium influx that stimulates a cascade of intracellular events, resulting in apoptosis or necrosis (see Fig. 1). Reactive oxygen species (ROS) also play a role in brain injury caused by neonatal hypoglycemia [59]. The ability of mitochondria to produce ROS is increased after hypoglycemia in the immature brain. This, in turn, can alter brain structure and function because of oxidant injury sustained by mitochondrial proteins, DNA, or signal transduction pathways in brain [59]. In addition, hypoglycemia is known to release adenosine, which in turn results in neuronal death (see Fig. 1). Hence adenosine receptor subtype antagonists have been observed to reverse hypoglycemia-induced neuronal injury [60]. This is of importance, given that caffeine is an adenosine receptor A1 and A2a receptor antagonist and known to reduce the sensitivity to hypoglycemia [61]. The effect of maternal consumption of caffeine on the infant’s response to hypoglycemia is unknown.

Transient anoxia/hypoglycemia is associated with a marked increase of excitatory neurotransmission, which shares similarities with the mechanisms underlying long-term potentiation (LPS), and increases synthesis of excitatory receptor subunits [58]. Both hypoxia and hypoglycemia increase the Ca\(^{++}\) influx, which can control the activation of proteolytic enzymes, apoptotic genes, and production of reactive oxygen species directly [62], thus mediating the ultimate neurological insult encountered.

Immature brain also may be more sensitive to limitations of substrate availability because of the presence of minimal cerebral reserves of high-energy phosphates [63]. Thus, there may be enhanced vulnerability of the fetus and newborn to excitotoxic brain injury during hypoglycemia. Acute insulin-induced hypoglycemia leads to specific changes in the cerebral NMDA receptor-associated ion channel in the newborn piglet [64].

In animal studies, many hypoglycemia-induced biochemical alterations in neonatal brain are similar to adults, yet the neurological function and electrical activity are preserved in the neonatal brain at lower plasma glucose concentrations [65]. Although the biochemical changes causing CNS injury in hypoglycemia and hypoxic–ischemic injury are the same, MRI findings suggest that hypoglycemia induces cerebral damage by a mechanism separate from the effects of cerebral hypoxia–ischemia (HIE) [10,66,67]. Severe perinatal hypoglycemia illustrates diffuse cortical and subcortical white matter damage, with the parietal and occipital lobes being affected most severely [42,68] (Fig. 3). This specific pattern of injury correlates with the pathological reports of neonatal hypoglycemia, suggesting that the pattern of damage results from regional hypoperfusion and excitotoxicity with cell type-specific injury [10]. The MRI changes from HIE typically involve parasagittal lesions involving the parieto–occipital cortex that is not limited to the posterior pole of the brain. Occipital brain injury associated with neonatal hypoglycemia can result in long-term disability, epilepsy, and visual
impairment. MRI brain imaging can delineate the extent of brain injury and help prognosticate the long-term outcome of these infants. Transient neonatal hypoglycemia in some full-term infants is reported to be associated with patchy hyperechogenic white matter abnormalities in the frontal and parieto–occipital lobes on cranial ultrasound and cerebral MRI[42,51], the functional significance of which needs to be ascertained. Pathological studies document superficial cerebral cortex, dentate gyrus, hippocampus, and caudate nucleus being most affected[51]. Clinical relevance of these findings, however, is not defined by long-term neurodevelopmental examinations in these full-term infants. Similar studies are nonexistent in late preterm infants, providing a fertile ground for future investigations.

Interventions targeted at hypoglycemia

There are no definitive clinical or laboratory indicators of injury specific to glucose deficiency. Therefore, clinicians must maintain a high index of suspicion to the risk of hypoglycemia in late preterm infants and have a low threshold for investigating and diagnosing hypoglycemia, with frequent monitoring of plasma/blood glucose concentration toward maintaining safe glucose concentrations. Additionally, there is no absolute cut-off value or duration of hypoglycemia that dictates neurological injury. Further, when low blood glucose values are detected, the exact duration of the detected low value cannot be surmised with accuracy unless a normal value was obtained previously at a given time. During the period of transition, late preterm and term infants are treated for blood glucose values less than 45 mg/dL or in the presence of symptoms. Hypoglycemia therapy includes:

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Fig. 3. MRI of brain in neonatal hypoglycemia. Severe neonatal hypoglycemia with seizures 5 days after birth. (A) T2-W image. (B) T1-W image. (C) DWI. On both the T2-W and T1-W images, the occipital cortex of both hemispheres shows increased and decreased signal intensity, which may be confused with subcortical white matter (arrows). On the DWI, a clear diffusion restriction is demonstrated. (Adapted from Triulzi F, Parazzini C, Righini A. Patterns of damage in the mature neonatal brain. Pediatr Radiol 2006;36(7):608–20; with permission.)
• Early feeds-formula
• Glucose infusion (200 mg/kg bolus plus 6 to 8 mg/kg/min)
• Hydrocortisone (intravenous dose: 1–5 mg/kg/day divided every 12–24 hours; not recommended for hyperinsulinemia)
• Glucagon (300 μg/kg, maximum dose 1 mg)
• Epinephrine (0.1 to 1 μg/kg/min)
• Diazoxide (5 to 15 mg/kg/d in two to three doses)
• Octreotide (IV 1–10 μg/kg/d in one to two doses, can be increased gradually to a maximum of 40 μg/kg/d divided in 3 to 6 doses.)

Early feeds are the best intervention; however, in infants being breast fed, the establishment of adequate milk let down and ingestion may take 1–2 days. In these cases, introduction of formula may create some controversy with respect to the success in subsequently establishing breast feeding. This has led to introduction of oral glucose solution (10 to 20 mL/kg) in late preterm and term infants. The risk of rebound hypoglycemia, however, is a possibility and needs close monitoring. Intravenous therapy should be initiated if this intervention does not succeed. This should consist of 200 mg/kg of dextrose bolus followed by a rate of 6 to 8 mg/kg/min dextrose [69,70]. Poor feeding in the presence of low glucose may constitute a symptom leading to introduction of intravenous fluids sooner. Treatment also includes treating the underlying conditions and providing a neutral thermal environment. Glucose levels are monitored every 20 to 30 minutes until stable. The bolus may be repeated if hypoglycemia persists, followed by increasing glucose delivery by 2 mg/kg/min to a maximum of 12 to 15 mg/kg/min. Blood sugar monitoring is continued for the first 24 to 48 hours or until stabilized, especially when any of the risk factors for hypoglycemia are present. Once the glucose level is stabilized, the intravenous infusion should be withdrawn, monitoring blood glucose concentration closely. Hypoglycemia secondary to maternal conditions usually resolves within 48 to 72 hours. Most infants with neonatal conditions that increase the risk for persistent hypoglycemia are symptomatic of the primary disorder. Thus, if the blood glucose fails to respond to adequate intravenous glucose delivery, other causes of persistent hypoglycemia must be entertained and the treatment tailored accordingly.

Prevention of neurological impairment

In late preterm infants with limited ketogenic capability, there is evidence that prolonged hypoglycemia is associated with neurological impairment. Although the entire health care system is not geared toward managing these infants as a separate category from term infants in the well baby nursery and the infants in NICUs, it is imperative that a separate structure be provided to support adequate monitoring and intervention in these infants toward preventing irreversible neurological sequelae. Early discharge of the late preterm infants
can result in rehospitalizations and increased morbidity. The associated risk of permanent brain damage leaves the physician vulnerable to litigation.

**Future investigations**

The recent awareness of the increasing trend in late preterm births and the poor transition faced by these infants should galvanize increasing investigations targeted at their outcomes. In particular, most of the investigations related to hypoglycemia undertaken so far have involved all infants with mixed diagnosis. Some have been retrospective with inadequate controls, or have involved small numbers with inadequate power to test the stated hypothesis. Given the advances in brain imaging and the development of noninvasive glucose monitoring devices, the time is ripe to conduct a well-controlled, adequately powered prospective study on late preterm infants who present with hypoglycemia during transition and follow them closely along with adequate brain imaging techniques and a battery of neurological and developmental testing to determine the long-term outcome of this subpopulation of infants. Timely interventions targeted toward amelioration of neonatal hypoglycemia need to be considered in the study design and analysis. Subsequent investigations targeted at preventing or reversing hypoglycemia-induced brain injury can be contemplated. Until then, anticipation preempting prompt diagnosis and timely intervention are the only ways to prevent adverse long-term neurological outcomes in late preterm infants who are discharged home, sometimes before they have established adequate milk intake during breast feeding.

**References**


