IJIMM, Volume 3, Issue 11, 2025 ISSN: 2995-5319
http://medicaljournals.eu/index.php/IJIMM/issue/view/3

INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

Mechanism of Hypoglycemia Development in Premature Infants, Treatment Approaches

Sagdullayeva Ma'fura Abdukarimovna
PhD Associate Professor, Department of Propaedeutics of Children's Diseases No. 1, Tashkent State Medical University

Isaqova Shirina Sodiqjon kizi
5th grade student Tashkent State Medical University (Email:isaqiva.shirina@icloud.com)

Khoshimova Gulnora Yulduzovna
Head of the Department of Pediatrics, Yangiyul Public Health Technical School

Azimova Mukhabbat Obidovna
Head of the Department of Obstetrics, Yangiyul Public Health Technical School

Abstract: Glucose, like oxygen, is essential for all living organisms and serves as the main energy source for the fetus and newborn during pregnancy. The placenta provides a constant supply of glucose to the fetus, whereas birth marks a sudden interruption in substrate delivery and significant metabolic adaptation.

Hypoglycemia is one of the most common pathologies encountered in neonatal intensive care units, affecting a wide range of newborns. Preterm infants, small-for-gestational-age (SGA) infants, and those with intrauterine growth restriction (IUGR) are particularly vulnerable due to limited metabolic reserves and associated morbidities.

Nearly 30–60% of these high-risk neonates develop hypoglycemia that requires immediate intervention. Preterm infants are especially prone to hypoglycemia and its related complications because of limited glycogen and fat stores, inability to generate new glucose via gluconeogenesis, relatively large brain size with high metabolic demands, and immature counterregulatory responses to hypoglycemia.

Keywords: hypoglycemia, gluconeogenesis, hypoglycemic brain injury, neurodevelopmental outcome, intrauterine growth restriction.

Introduction

Hypoglycemia [Gk. hypo (below or under) + glykys (sweet) + haimah (blood)] is a term coined by Harris in the late 19th century to describe low blood sugar levels ([1]). Over the past century, there has been a large body of literature examining the effects of low blood glucose, particularly in newborns, but there has been little consensus on its definition or the acceptable range of glucose levels in different types of newborns. Since then, hypoglycemia has been measured and defined as a range of clinical manifestations and laboratory values, and the approach to this problem has gradually been adapted to the specific physiological adaptations of the infant. The association of hypoglycemia and neurodevelopmental abnormalities in premature infants was first noted in 1937. This led to the classification of hypoglycemia as “mild” at 40 to 50 mg/dL (2.2 to 2.8 mmol/L), moderate (20 to 2.4 mg/dL), and “severe” at 20 mg/dL (1.1 mmol/L) (2). One group of investigators proposed a normal low glucose level of 30 to 35 mg/dL (1.67 to 1.94 mmol/L) during the first 24 hours of life; 45 mg/dL (2.5 mmol/L) after feeding; and 40 to 50 mg/dL (2.22 to 2.78 mmol/L) after the end of 24 hours of life (3). Since then, many operational thresholds have been described. Both the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) have attempted to reach a consensus on the safe range of glucose in newborns. It is currently accepted that plasma glucose levels should fall to

30 mg/dL (1.67 mmol/L) within the first 2 h of life and then rise to at least 45 mg/dL (2.5 mmol/L) before stabilizing at around 12–24 h (4). In recent decades, there has been interest in studying energy requirements of small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) preterm infants. Early studies in the early 1970s suggested that these infants were not only more susceptible to hypoglycemia but also had a higher risk of delayed recovery and poor long-term prognosis (6 , 7). The estimated incidence of hypoglycemia in SGA infants is approximately 70% (8). One study found that 15% of hypoglycemic infants born prematurely were AGA, and the remainder were large for gestational age (LGA) or SGA (9). In the 1970s, Kornblath *et al.* suggested that a lower operating limit of blood glucose for premature infants might be 20 mg/dL, as their lack of symptoms suggested that their brains were less sensitive and better adapted to low glucose values (3). Transabdominal cordocentesis was performed to measure fetal blood glucose levels and then compared with maternal serum glucose concentrations, with fetal venous glucose levels ranging from 72 to 90 mg/dL (4 to 5 mmol/L). As the infant approached term, a widening of the glucose gradient between the maternal and fetal circulations was observed (10). Intrauterine growth restriction has been shown to be closely related to the degree of hypoxia, but not to hypoglycemia. Hypoglycemia itself is more likely to be the result of reduced glucose production due to small glycogen stores and excessive utilization (11). There is a strong correlation between fetal and maternal glucose values in early pregnancy. However, as the third trimester approaches, the gradient increases as fetal glucose utilization increases, and maternal values exceed fetal values (12). This suggests that preterm and SGA infants should have serum glucose concentrations similar to their mothers. In severely growth-restricted fetuses, this gradient is widened to allow for facilitated diffusion and is a function of clinical severity, so fetal blood glucose values are related to GA and maternal glucose (13).

Normal glucose physiology in the newborn

In the newborn, glucose is maintained by a variety of processes, including gluconeogenesis, metabolism, insulin secretion, and “counter-regulatory” hormones. This homeostasis is maintained not only by insulin and glucagon, but also by hormones such as catecholamines, growth hormone, and cortisol, which determine its uptake and utilization. Ingestion of food or infusion of glucose in the form of carbohydrates helps to increase the concentration of glucose in the body, which in turn activates glucokinase and β-cell glycolysis (14 , 15). This process ultimately produces acetyl-coenzyme A (acetyl CoA), a common end product not only of glycolysis but also of protein breakdown and lipolysis. Acetyl CoA enters the Kreb’s cycle, which then provides adenosine triphosphate (ATP) and supports all cellular functions (15 , 16). The endocrine β cells produce insulin and the α cells produce glucagon ; glucose is the primary energy source for the brain, and the fetal and neonatal brain is able to utilize ketone bodies, lactate, and even amino acids under extreme conditions (3 , 18). The neonatal brain is one of the most energy-efficient organs because it oxidizes almost all of the glucose supplied to it (19). Glucose transport across the blood–brain barrier (GLUT), as well as its passage across neuronal and glial lipid membranes, occurs by a process known as facilitated diffusion. Facilitated diffusion is an energy-independent pathway that moves glucose from the blood into the cytoplasm, and the process is bidirectional. Thus, ongoing glycogenolysis and gluconeogenesis often contribute to glucose release from the cell. In mature placentas during pregnancy, insulin does not modify or promote glucose uptake by either the mother or the fetus (20). The large surface area of the choriodecidual villi is in direct contact with maternal blood, resulting in a shared glucose pool for the mother–infant pair (19 , 21). Most of the glycogen deposition in fetal tissues occurs during the second half of pregnancy. Adequate glucose transport from mother to fetus is largely determined by umbilical cord blood flow, as there is no apparent difference in the expression of the glucose transporter-1 (GLUT-1) protein in placentas (22). The facile transfer of glucose is mediated by the GLUT family of proteins, of which about 14 have been identified to date. The protein and mRNA levels of GLUT1 increase in the placenta as the fetus matures (23). It has been shown to be responsible for the transfer of glucose from maternal blood into the cytoplasm of the syncytiotrophoblast and then into the extracapillary space in the fetal circulation, facilitating its release across the basement membrane (21). GLUT 1, 3, and 11 are located in the placenta and are essential for the growing fetus, while GLUT 2

and 4 are insulin-sensitive glucose transporters (20). GLUT 1 helps transport glucose across the blood–brain barrier (BBB) and works closely with GLUT 3 to promote glucose uptake in brain cells (24). GLUT GA plays a role in determining the large versus small phenotype for infants. Gestational diabetes causes increased maternal blood glucose levels and, therefore, increased transplacental transport to the placenta and fetus, which leads to excessive growth via insulin-like growth factor-1 (IGF-1). In these pregnancies, elevated GLUT 1 levels were found, while no changes were found in GLUT 3 and GLUT 4, suggesting that fetal hyperglycemia in diabetic pregnancies is directly related to GLUT 1 levels. Animal studies of IUGR pregnancies have shown that the fetus has relative hypoglycemia, which further enhances facilitated diffusion (20 , 21 , 25–28).

The transition from fetal to neonatal life is one of the most complex and critical physiological adaptations in human life (29 , 30). After the placental glucose supply is interrupted, plasma glucose reaches its lowest level within the first 2 h after birth, which triggers the release of counter-regulatory hormones that are essential for gluconeogenesis during the first 6–24 h of life (31). Catecholamines (epinephrine and norepinephrine), which play a crucial role in adaptation to various stressors outside the uterus, increase (29 , 32). Infants born by cesarean section have significantly lower catecholamine levels than those born by spontaneous vaginal delivery and are therefore more susceptible to hypoglycemia. Surprisingly, some premature infants have higher catecholamine levels in their breast blood than term infants (29). Catecholamines help maintain blood pressure and normothermia by stimulating alpha receptors, which increases blood pressure and promotes brown fat utilization. They also help prevent hypoxia by inducing alveoli to increase surfactant production (29). Epinephrine stimulates hepatic glycogenolysis and gluconeogenesis, which helps prevent hypoglycemia (33). The “cortisol surge” that occurs with catecholamine release increases vascular β receptor density and increases gluconeogenesis, which further increases serum glucose levels (29 , 34). Preterm infants (33–36 weeks' gestation) have been shown to have higher serum cortisol levels than term infants (35), but in preterm infants born at 24–36 weeks' gestation, GA levels are inversely proportional to gestational age and remain elevated from 2–6 days of life. However, infants born at less than 28 weeks' gestation, and therefore at lower GA, do not become more ill than those born at higher GA.

Etiology

Healthy infants experience an expected drop in blood glucose concentrations immediately after birth as part of the normal physiological transition to extrauterine life. The sudden clamping of the umbilical cord at birth disrupts the infant's attachment to the placenta, which then relies on the placenta for glucose and other metabolites to meet its energy needs in utero. The continuous supply of exogenous intravenous glucose from the placenta is abruptly interrupted, and the infant's blood glucose concentration falls within the first hours of life. For most healthy infants, this transient neonatal hypoglycemia is brief, transient, and often asymptomatic. [4] [11] Infants are at risk for more severe or prolonged hypoglycemia due to one or a combination of the following major mechanisms: inadequate glucose supply , low glycogen or fat stores, or impaired glucose production mechanisms; increased glucose utilization due to excessive insulin production or increased metabolic demand; or failure of opposing regulatory mechanisms (i.e., pituitary or adrenal insufficiency). [12] [11] Neonatal hypoglycemia most commonly affects the following groups of infants : [3]

- Uterus inside to grow restriction or pregnancy at the age of for babies relatively small
- For babies of mothers with diabetes or babies of a large gestational age
- Premature babies (34 to 36.6 weeks gestation)

Premature, intrauterine growth restricted, and small-for-gestational-age infants are at increased risk of hypoglycemia due to the fact that they are born with reduced glycogen stores, reduced adipose tissue, and increased metabolic demands due to their relatively large brain size. [1] [12] Very low birth weight (<1000 g) premature infants have low levels of enzymes involved in gluconeogenesis; therefore, their ability to produce endogenous glucose is reduced, increasing the risk of severe or prolonged hypoglycemia. [12] Infants of mothers with diabetes mellitus (DM) and infants born large for

gestational age (LGA) have increased fetal hyperinsulinism and increased peripheral glucose utilization, which puts them at risk for hypoglycemia in the postpartum period. [1] [4] [12] The placenta provides the fetus with a direct source of glucose through facilitated diffusion, so that fetal glucose concentrations are proportional to maternal levels. Prolonged elevated maternal glucose concentrations result in fetal hyperglycemia and overstimulation of the pancreas to increase endogenous fetal insulin production. [12] High fetal insulin levels persist after birth and, in the absence of a continuous exogenous glucose source, lead to increased glucose utilization and decreased blood glucose concentrations. [12] IDMs experience a reduced ability to mobilize glycogen stores after birth and experience relative adrenal insufficiency with decreased catecholamine levels, which contributes to the risk of hypoglycemia. Infants experiencing perinatal stress (e.g., fetal distress, perinatal ischemia, maternal preeclampsia / eclampsia , sepsis, hypothermia) or infants with congenital heart disease have increased metabolic energy requirements, which puts them at risk for hypoglycemia. [1] [4] [12] Perinatal stress induces a state of "hypoglycemic hyperinsulinism" that can last for days to weeks, resulting in persistently low glucose concentrations, requiring ongoing intervention to maintain glycemia. [1] Other iatrogenic causes of transient neonatal hypoglycemia include intrapartum administration of maternal medications (e.g., beta-adrenergic tocolytic agents, valproic acid, propranolol, and conduction anesthetics), delayed feeding, and exogenous insulin administration. [12] [11] Low glucose concentrations after the first 48 hours of life raise concerns about an underlying disease as the etiology of hypoglycemia. The main physiological mechanisms that cause pathological or persistent hypoglycemia are similar to those described above: hyperinsulinism (e.g., congenital hyperinsulinism, Beckwith-Widman syndrome, Soto syndrome), inadequate energy supply (i.e., inborn errors of metabolism, acidosis or free acidosis, hypoglycemia, hypoglycemia); cortisol or growth hormone deficiency (e.g., Costello syndrome, hypopituitarism, congenital adrenal hyperplasia). Causes of persistent neonatal hypoglycemia include [12] [10] :

- Congenital hyperinsulinism
- Congenital syndromes: Beckwith-Wiedemann syndrome, Soto syndrome, Costello syndrome
- Endocrine diseases: congenital hypopituitarism, congenital adrenal hyperplasia, hypothyroidism
- Inborn errors of metabolism: maple syrup urine disease, glycogen storage disorder, hereditary fructose intolerance, galactosemia, fatty acid oxidation disorder.

Epidemiology

The incidence of hypoglycemia in newborns is variable and depends on several factors, including the number of infants, the frequency and timing of glucose testing, the testing method, and the definition of hypoglycemia used. A 2006 study by Harris et al., which sought to determine the incidence of hypoglycemia (blood glucose <47 mg/dL) in the first 48 hours of life in infants at risk for hypoglycemia at >35 weeks' gestation, according to AAP guidelines, found that 25% of all deliveries were at risk for hypoglycemia; 51% of at-risk infants experienced at least one episode of hypoglycemia. [1] [13] The fetus depends on maternal metabolism and the placental circulation to provide the glucose, ketones, free fatty acids, and amino acids needed to meet its energy needs. [2] The placenta provides a direct source of glucose to the fetal circulation. [2] [5] At birth, the umbilical cord clamp abruptly interrupts this continuous source of glucose, resulting in a rapid drop in blood glucose levels during the first 2–3 hours of life. [1] [2] [5] The low blood glucose concentration leads to increased secretion of insulin and other hormones (including catecholamines, glucagon, and corticosteroids), which stimulate glucose production through gluconeogenesis and glycogenolysis, and increase fatty acid oxidation. This provides the infant with an endogenous source of glucose and other energy substrates needed to fuel its metabolism , [1] resulting in a gradual rise in blood glucose levels over the next few hours to days . [5] The low glucose levels also stimulate the newborn's appetite and help the newborn adjust to intermittent feeding. [1] Any mechanism that disrupts this sequence of physiological changes will expose the infant to more severe or prolonged low glucose levels. The risk of hypoglycemia is highest in the first hours after birth. [5] [12] Persistent hypoglycemia results from excessive insulin secretion, cortisol or growth hormone deficiency , or inborn errors of metabolism. [4]

[12] The clinical presentation of hypoglycemia in newborns is variable. An otherwise healthy infant may remain asymptomatic during a period of transient hypoglycemia despite very low blood glucose levels. Clinical symptoms are independent of blood glucose levels.

Signs of neonatal hypoglycemia [2] [11] include :

- Sweating
- Feeding difficulties, poor sucking
- Weak or loud crying
- Tremors
- Hypothermia
- Anger
- Lethargy/stupor
- Hypotension
- seizures
- Coma
- Cyanosis

Evaluation

Two major academic societies, the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES), provide conflicting guidelines for screening and management of at-risk infants and neonatal hypoglycemia. The most recent AAP guidelines recommend screening preterm and term infants with symptoms of hypoglycemia and asymptomatic infants at high risk of hypoglycemia within the first 12 to 24 hours of life. "At-risk" infants include those born prematurely (34 to 36.6 weeks of gestation), term infants who are small for gestational age, infants of mothers with diabetes, and infants born for gestational age. [3] The guidelines state that "routine blood glucose testing and monitoring is not necessary in healthy infants born after a normal pregnancy and delivery." [3] The Pediatric Endocrine Society (PES) recommends screening all infants with risk factors for prolonged or pathological hypoglycemia, including [4] :

- Symptomatic hypoglycemia
- Great for pregnancy
- Perinatal stress
- ✓ Perinatal hypoxia/ischemia, fetal distress
- ✓ Maternal preeclampsia or eclampsia
- ✓ Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia
- Premature or post-term birth
- Baby of a diabetic mother
- Family history of genetic hypoglycemia
- Congenital syndrome (e.g., Beckwith-Wiedermann), abnormal physical features (e.g., midline facial defects)

According to the PES guidelines, infants who fail to maintain a pre-meal blood glucose level of >50 mg/dL or >60 mg/dL after a meal during the first 48 hours of life are at risk for persistent hypoglycemia and require further evaluation before discharge. [4] The PES recommends that infants at risk for persistent hypoglycemia be evaluated for the underlying etiology after the first 48 hours of life

, to rule out transient low glucose levels (i.e., transient neonatal hypoglycemia) . [4] The PES recommends that infants be evaluated for the following to rule out persistent causes of hypoglycemia [4] :

- Symptomatic hypoglycemia or severe hypoglycemia requiring treatment with intravenous dextrose
- Infants who cannot maintain blood glucose concentrations >50 mg/dl in the first 48 hours of life and >60 after 48 hours.
- Family history of a genetic form of hypoglycemia
- Congenital syndrome (e.g., Beckwith-Wiedermann), abnormal physical features (e.g., midline facial defects)

Point-of-care testing (POCT) offers a rapid and cost-effective method for testing for hypoglycemia. [5] However, these methods have limitations. Most standard devices use non-enzymatic methods to measure blood glucose concentrations, which are less accurate at lower glucose values than laboratory assays using glucose oxidase methods (the gold standard). [5] Whole blood samples (used in POCT) have glucose concentrations that are 10% to 18% higher than those in plasma, depending on the hematocrit. [5] Therefore, abnormally low glucose values on POCT require confirmation by measuring plasma glucose concentrations using clinical laboratory methods. [4] [10] Measurement of bicarbonate, lactic acid, beta-hydroxybutyrate, free fatty acids, insulin, and carnitine during hypoglycemia (blood glucose <50 mg/dl) in infants with persistent hypoglycemia is helpful in diagnosing hypoglycemia-related disorders.

Hypoglycemia Etiopathogenesis.

Hypoglycemia mainly working of release decrease or glucose from reserves excess use as a result to the surface comes . So glycogen and oil reserves less was new born in babies gluconeogenesis way through glucose harvest to do ability limited or to insulin related diabetes with sick mother's in the baby what happened such as glucose peripheral tissues by too much outside many consumer goods in doing hypoglycemia appearance will be (37-39) From birth then euglycemia thin controllable metabolic changes and hormones secretion combination with is stored . Very less weighty early born babies glycogen and adipose tissue less reserves with is born . This situation is further complicated by the presence of several enzymes involved in gluconeogenesis. Phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase, fructose-1,6-diphosphatase, and pyruvate carboxylase are expressed at very low levels, limiting their ability to perform gluconeogenesis. Premature infants and those with IUGR are at increased risk of hypoglycemia in the neonatal period (40) . Various congenital disorders, such as Beckwith-Wiedemann syndrome, Turner syndrome, Down syndrome, Costello syndrome, congenital hypopituitarism, and congenital adrenal hyperplasia, also predispose the infant to hypoglycemia. Inborn errors of metabolism, such as maple syrup urine disease, glycogen storage disorder, fructose intolerance, and fatty acid enzyme deficiency, can also lead to persistent hypoglycemia. Newborns have poorly developed counter-regulatory mechanisms to combat hypoglycemia, making them very vulnerable. The hypoglycemic newborn protects itself by reducing insulin secretion and increasing glucagon, epinephrine, growth hormone, and cortisol secretion, which leads to glucose production and mobilization of fatty acids from adipose tissue. Increased glucose production occurs initially from glycogen breakdown (up to 1-2 hours) and then from protein breakdown with increased cortisol levels. This process is manifested by increased plasma levels of the gluconeogenic amino acids, alanine, and glutamine. Hypoglycemia occurs with excessive insulin production (overuse), poor gluconeogenesis (underproduction), or failure of opposing regulatory mechanisms (pituitary or adrenal insufficiency).

Treatment of hypoglycemia in preterm infants.

The diagnosis and treatment of hypoglycemia depend largely on the cause and severity of hypoglycemia, the clinical presentation, and the underlying etiology. Thus, the treatment plan should be individualized for each infant. In the past, the Whipp triad of clinical signs, low glucose values, and

treatment response was used (38 , 41), but recently we have moved more toward a precise biochemical diagnosis. The key to diagnosis is to determine whether the hypoglycemia is transient or persistent. Based on this conclusion, the infant with persistent hypoglycemia should be referred to a tertiary care center and a comprehensive evaluation should be performed as described below. The infant may present with neurogenic or neuroglycopenic signs and symptoms. Neurogenic indicates an active catecholamine-driven response, including tachycardia, vomiting, sweating, tremors, and retching. Neuroglycopenic signs are the result of neuronal glucose deficiency, manifested by hypotension, apnea, and seizures, with coma being the worst outcome (43). Biochemical assessment of blood glucose levels is more accurate than clinical assessment alone. Plasma glucose values are 10–18% higher than whole blood values (4). The Pediatric Endocrine Society (PES) and the American Academy of Pediatrics (AAP) recommend a glucose level ≥40 mg/dL (mmol/L) within the first 4 hours; treatment of values ≥45 mg/dL (mmol/L) after feeding for 4–24 hours and ≤40 mg/dL (mmol/L) parenterally (15 , 19 , 44). The PES recommends a similar strategy, suggesting levels >50 mg/dL (mmol/L) within the first 48 hours and >60 mg/dL (mmol/L) thereafter (19). Persistent hypoglycemia requires emergency medical attention and prompt intervention, as delay can lead to complications and blood glucose levels should be maintained at >70 mg/dL (mmol/L) (19). Normal term infants should be fed as much as possible, resulting in a blood glucose level of 30 mg/dL (1.67 mmol/L) for 30–60 mL of standard infant formula. Blood glucose should be monitored before and after feedings for at least 12–24 h. If normoglycemia is not achieved, the next step is parenteral dextrose administration, starting with a “mini bolus” of 200 mg/kg of 10% dextrose in water (2 mL/kg of D 10 W), followed by continuous intravenous infusion, and blood glucose rechecked after 30 min (1 h). The goal is to provide a continuous glucose infusion rate (GIR) of 6–8 mg/kg/min (3), which is especially important in premature and low-birth-weight infants because it is equivalent to the amount of glucose provided by the liver through gluconeogenesis (3 , 10 , 45). For infants born to mothers with diabetes, a lower dextrose infusion rate of 3–5 mg/kg/min may be appropriate, providing minimal stimulation of the pancreas to produce insulin (19). With such interventions, if the infant does not achieve normoglycemia, it is reasonable to increase the GIR to 8, 10, 12, and then 15 mg/kg/min over 24 hours (3). Dextrose concentrations greater than 12.5% require central venous access (46). It may also be prudent to obtain arterial access in these infants to avoid repeated needle sticks to the fingers, toes, and heels of these premature infants. Continuous glucose monitoring (CGM), although still experimental, is emerging as the new standard for monitoring blood glucose in young infants. The CGM device measures and updates blood glucose values every 5 min, providing real-time information (42 , 47). Once a reliable method of assessing the infant's blood glucose level is established, it is important to titrate the dextrose infusion appropriately. With effective therapy, most infants achieve euglycemia within 2–4 days. A period of hypoglycemia lasting 5–7 days suggests a diagnosis of persistent neonatal hypoglycemia and requires alternative treatment options (46). The PES recommends considering persistent hypoglycemia after 48 h and recommending follow-up. This includes laboratory tests such as insulin levels, metabolic profile, genetic studies, and imaging to look for pathology in the pancreas, adrenal glands, and pituitary glands (19). Corticosteroids such as hydrocortisone at doses of 5–15 mg/kg/day or prednisone 2 mg/kg/day reduce peripheral glucose utilization and are therefore considered second-line therapy for persistent hypoglycemia after glucose infusion (3 , 48–51) . Glucagon, produced by pancreatic α cells, is a counterregulatory hormone that initiates gluconeogenesis and glycogenolysis during hypoglycemia (52), helping to raise blood glucose levels if the infant has adequate glycogen stores. However, its efficacy is limited in infants of mothers taking beta-blockers such as atenolol or metoprolol (53). In infants with adequate glycogen stores, glucagon, administered as an infusion at 30 μg/kg or 300 μg/kg/min, promotes glycogenolysis and gluconeogenesis (16). Glucagon is particularly useful in premature infants, infants of diabetic mothers, during transport of critically ill infants, and when short-term treatment is required. Somatostatin, which inhibits insulin and growth hormone release, is usually reserved as a last resort when other treatments have failed to raise and maintain blood glucose levels (48). Octreotide, a long-acting analog of endogenous somatostatin, acts directly on voltage-gated calcium channels, where diazoxide is used (14 , 54). It is used as a continuous infusion at a dose of 3–10 μg/kg/day (14), but

is not currently FDA-approved and there are concerns that it may impair neonatal growth. Hyperinsulinism associated with genetic defects in SUR, where uncontrolled insulin production occurs, usually responds well to diazoxide treatment (16 , 48). Diazoxide, a high-affinity K_{ATP} channel opener, acts by stabilizing these channels and blocks insulin secretion (55), thereby helping to manage persistent hyperinsulinism. If the hyperinsulinism is secondary to abnormalities in the SUR and Kir 6.2 subunits of the glucose channel, a significant response to diazoxide may not be seen. Diazoxide is usually administered in a dose range of 10–15 mg/kg/day, with responders showing an effect within 2–4 days (56). Nifedipine is another unspecified drug for neonatal use in cases of failure to respond to diazoxide and octreotide (57). Nifedipine was used in infants at a dose of 0.3–0.8 mg/kg/day by Bas et al . (58) and has been effective when other treatments have failed, but it is not the mainstay of treatment because of its cardiovascular side effects.

Recently, oral dextrose gel has emerged as a promising new treatment for neonatal hypoglycemia, particularly in preterm infants. Several studies have been conducted using dextrose gel. In the Sugar Babies trial, Harris *et al.* (64) were able to effectively demonstrate improvement in hypoglycemia within the first 48 hours; promote bonding and prevent separation of mothers from their infants. A subsequent study by the same group demonstrated no effect on neurodevelopmental outcomes, casting doubt on earlier promising results (63). Several studies have shown that oral dextrose gel is suitable for the treatment of hypoglycemia in stable infants who can be fed (59–62). Dextrose gel is used not only to prevent and treat hypoglycemia, but also to promote breastfeeding and to bond mothers and infants. Neuroradiological studies to investigate the anatomical location of brain damage due to hypoglycemia, using various MRI modalities, have shown cortical abnormalities in the posterior cerebral cortex with or without subcortical or periventricular lesions (65). There is sparing of the parietal and occipital lobes (66 , 67). Rarely, thalamic lesions or basal ganglia lesions may also be present. Therefore, in the presence of a history of prolonged and severe hypoglycemia, further MRI studies are indicated (65). Hypoglycemic brain injury does not necessarily require vascular monitoring, so it may sometimes be difficult to distinguish hypoglycemic from hypoxic brain injury (68). The Babies and Blood Sugar Study (BABIES) studied the effects of hypoglycemia on the EEG using bedside amplitude-integrated electroencephalography (aEEG) to assess real-time neuronal damage due to hypoglycemia (79). Glucose levels were also measured, as were nonglucose brain fuels such as lactate, beta-hydroxybutyrate, and glycerol. These studies did not show significant EEG abnormalities even during periods of low glucose levels and use of other brain fuels, suggesting that aEEG is not a useful tool (79). The normal brain derives more than 50% of its energy needs from glucose oxidation (44). In SGA infants, there is a strong association between hypoglycemia and smaller head circumference measured at 12 months, 18 months, and 5 years of corrected age (8). Glial proliferation is known to occur in the third trimester of fetal life and continues after birth (80). Hypoglycemia delays astrocyte proliferation in preterm infants, and up to approximately 4–5 weeks, the sensorimotor cortex, thalamus, midbrain, brainstem, and cerebellar vermis are most sensitive to hypoglycemic injury, except for the occipital cortex (18 , 819) . Hypoglycemic brain injury has been associated with smaller head circumference and poorer cognitive performance, as demonstrated in a cohort of 249 very low birth weight infants (82). Twelve percent (30/249) of these infants had subnormal or -2 SD age-adjusted head circumference at birth, 23% (57/249) had corrected GA at term, and 13% (33/249) had corrected GA at 8 months. These children had low intelligence quotient (IQ) and low receptive language scores (82). In summary, the duration, severity, and number of hypoglycemic episodes are closely related to the outcome of hypoglycemia. This may manifest as seizures or coma within hours of life or may manifest later in childhood as delayed milestones, developmental delays, poor Bayley scores, motor and cognitive performance, or poor test scores in grades 4 or 5.

Differential Diagnosis.

Symptoms of hypoglycemia in the newborn are nonspecific and overlap with other conditions, including prematurity, sepsis, hypoxic-ischemic encephalopathy, and hyponatremia. As mentioned above, although rare, persistent causes of hypoglycemia should be ruled out.

Severe, prolonged hypoglycemia in the neonatal period can have devastating consequences, including long-term neurodevelopmental disabilities, cerebral palsy, and death. Infants with congenital causes of persistent hypoglycemia have significantly higher morbidity and mortality rates: 25 to 50% have developmental defects. [4] Nervous tissue can survive prolonged periods of low blood glucose levels by utilizing alternative energy substrates (ketones, amino acids, lactate) to meet its metabolic needs. [4] [9] It has been hypothesized that the use of these alternative metabolites may have a neuroprotective effect on the immature neonatal brain. [11] However, eventually, a glucose supply must be established. In 1967, Anderson et al. published a series of pathological findings in 6 infants with severe, prolonged hypoglycemia during the first week of life. [9] The authors reported that severe, prolonged hypoglycemia caused widespread degeneration of the central nervous system and, if untreated, was ultimately fatal. [9] Brain damage was less severe in infants treated with exogenous glucose. [9] Thus, early recognition of conditions that lead to persistent hypoglycemia is essential. Although we continue to strive for a precise definition of hypoglycemia, it remains one of the most common causes of morbidity in 30–60% of premature infants, some of whom experience serious long-term complications (75 , 83 , 84). The degree, severity, and duration of hypoglycemia are directly proportional to poor outcomes if not treated promptly. Extremely premature infants are prone to several comorbidities due to perinatal risk factors. all of these effects are exacerbated by hypoglycemia. Preterm or premature infants are also at high risk if urgent measures are not taken to prevent hypoglycemia. Each case should be clinically assessed and divided into transient or persistent hypoglycemia, and all infants with persistent hypoglycemia should be referred to a tertiary care center where advanced diagnostic and therapeutic interventions are available. Glucose gel is a promising new tool in the treatment of near-term or late-term infants. Long-term neurodevelopmental follow-up should be obtained for all infants with severe and prolonged hypoglycemia, and this should include high-quality neuroimaging such as MRI scans.

References

1. Harris, S. (1924). Hyperinsulinism and dysinsulinism. *JAMA, 83*, 729–733. https://doi.org/10.1001/jama.1924.02660100003002
2. Hartmann, A. (1998). Hypoglycemia. *Journal of Pediatrics, 132*, 1–3. https://doi.org/10.1016/S0022-3476(98)70474-3
3. Cornblath, M., & Ichord, R. (2000). Hypoglycemia in the newborn. *Seminars in Perinatology, 24*, 136–149. https://doi.org/10.1053/sp.2000.6364
4. Heck, L. J., & Ehrenberg, A. (1987). Serum glucose levels in newborns during the first 48 hours of life. *Journal of Pediatrics, 110*, 119–122. https://doi.org/10.1016/S0022-3476(87)80303-7
5. Adamkin, D. H. (Committee on Fetus and Newborn). (2011). Postnatal glucose homeostasis in late- and preterm infants. *Pediatrics, 127*, 575–579. https://doi.org/10.1542/peds.2010-3851
6. Lubchenco, L. O., & Bard, H. (1971). Incidence of hypoglycemia in newborns classified by birth weight and gestational age. *Pediatrics, 47*, 831–838.
7. Parmelee, A. H. Jr., Minkowski, A., & Saint-Anne Dargassies, S. (1970). Neurological evaluation of the premature infant: A follow-up study. *Biology of the Neonate, 15*, 65–78. https://doi.org/10.1159/000240212
8. Duvanel, C. B., Fawer, C. L., Cotting, J., et al. (1999). Long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational-age preterm infants. *Journal of Pediatrics, 134*, 492–498. https://doi.org/10.1016/S0022-3476(99)70209-X
9. Gutberlet, R. L., & Cornblath, M. (1976). Neonatal hypoglycemia revisited, 1975. *Pediatrics, 58*, 10–17.
10. Kalhan, S., & Peter-Wohl, S. (2000). Hypoglycemia: What does it mean for the newborn? *American Journal of Perinatology, 17*, 11–18. https://doi.org/10.1055/s-2000-7296

11. Economides, D. L., & Nicolaides, K. H. (1989). Blood glucose and oxygen tension levels in small-for-gestational-age fetuses. *American Journal of Obstetrics and Gynecology, 160*, 385–389. https://doi.org/10.1016/0002-9378(89)90453-5

12. Bozzetti, P., Ferrari, M. M., Marconi, A. M., et al. (1988). The relationship between maternal and fetal glucose concentrations in humans from mid-term to term. *Metabolism, 37*, 358–363. https://doi.org/10.1016/0026-0495(88)90136-9

13. Marconi, A. M., Paolini, C., Buscaglia, M., et al. (1996). Influence of gestational age and fetal growth on the difference in maternal and fetal glucose concentrations. *Obstetrics & Gynecology, 87*, 937–942. https://doi.org/10.1016/0029-7844(96)00048-8

14. Sweet, C. B., Grayson, S., & Polak, M. (2013). Strategies for managing neonatal hypoglycemia. *Journal of Pediatric Pharmacology and Therapeutics, 18*, 199–208. https://doi.org/10.5863/1551-6776-18.3.199

15. Thompson-Abranch, & Havranek, T. (2017). Neonatal hypoglycemia. *Pediatrics in Review, 38*, 147–157. https://doi.org/10.1542/pir.2016-0063

16. de Lonlay, P., Giurgea, I., Touati, G., et al. (2004). Neonatal hypoglycemia: Etiology. *Seminars in Neonatology, 9*, 49–58. https://doi.org/10.1016/j.siny.2003.08.002

17. Schwitzgebel, V. M., & Gitelman, S. E. (1998). Hyperinsulinism of the newborn. *Clinics in Perinatology, 25*, 1015–1038.

18. Vannucci, R. C., & Vannucci, S. J. (2000). Glucose metabolism in the developing brain. *Seminars in Perinatology, 24*, 107–115. https://doi.org/10.1053/sp.2000.6361

19. Thornton, P. S., Stanley, C. A., De Leon, D. D., et al. (2015). Pediatric Endocrine Society recommendations for the evaluation and management of persistent hypoglycemia. *Journal of Pediatrics, 167*, 238–245. https://doi.org/10.1016/j.jpeds.2015.03.057

20. Hay, W. W. Jr. (2006). Placental-fetal glucose exchange and fetal glucose metabolism. *Transactions of the American Clinical and Climatological Association, 117*, 321–339.

21. Simmons, R. A. (2011). Cellular glucose transport and glucose handling during fetal and neonatal development. In Polin, R. A., Fox, W. W., & Abman, S. H. (Eds.), *Fetal and Neonatal Physiology* (4th ed., pp. 560–566). Philadelphia: Elsevier Saunders.

22. Jansson, T., Wennergren, M., & Illsley, N. P. (1993). Expression of glucose transporter protein in human placenta during pregnancy and intrauterine growth restriction. *Journal of Clinical Endocrinology & Metabolism, 77*, 1554–1562.

23. Arnott, G., Coghill, G., McArdle, H. J., et al. (1994). Immunolocalization of GLUT1 and GLUT3 glucose transporters in human placenta. *Biochemical Society Transactions, 22*, 272S. https://doi.org/10.1042/bst022272s

24. Thorens, B., & Mueckler, M. (2010). Glucose transporters in the 21st century. *American Journal of Physiology-Endocrinology and Metabolism, 298*, E141–E145. https://doi.org/10.1152/ajpendo.00712.2009

25. Gaither, K., Quraishi, A. N., & Illsley, N. P. (1999). Diabetes alters the expression and activity of the human placental GLUT1 glucose transporter. *Journal of Clinical Endocrinology & Metabolism, 84*, 695–701.

26. Jansson, T., Wennergren, M., & Powell, T. L. (1999). Placental glucose transport and GLUT1 expression in insulin-dependent diabetes. *American Journal of Obstetrics and Gynecology, 180*, 163–168. https://doi.org/10.1016/S0002-9378(99)70169-9

27. Kainulainen, H., Jarvinen, T., & Heinonen, P. K. (1997). Placental glucose transporters in intrauterine growth restriction and macrosomia. *Gynecologic and Obstetric Investigation, 44*, 89–92. https://doi.org/10.1159/000291493

28. Xing, A. Y., Challier, J. C., Lepercq, J., et al. (1998). Unexpected expression of glucose transporter 4 in human placental villous stromal cells. *Journal of Clinical Endocrinology & Metabolism, 83*, 4097–4101.

29. Hillman, N. H., Kallapur, S. G., & Jobe, A. H. (2012). Physiology of the transition from intrauterine to extrauterine life. *Clinics in Perinatology, 39*, 769–783. https://doi.org/10.1016/j.clp.2012.09.009

30. Ward Platt, M., & Deshpande, S. (2005). Metabolic adaptation at birth. *Seminars in Fetal & Neonatal Medicine, 10*, 341–350. https://doi.org/10.1016/j.siny.2005.04.001

31. Srinivasan, G., Pildes, R. S., & Cattamanchi, G., et al. (1986). Plasma glucose values in normal newborns: A new perspective. *Journal of Pediatrics, 109*, 114–117. https://doi.org/10.1016/S0022-3476(86)80588-1

32. Hume, R., Burchell, A., Williams, F. L., *et al.* (2005). Glucose homeostasis in the newborn. *Early Human Development, 81*, 95–101. https://doi.org/10.1016/j.earlhumdev.2004.10.005

33. Hume, R., Pazuki, S., Hallas, A., *et al.* (1995). Ontogenesis of the enzyme glucose-6-phosphatase in human embryonic and fetal red blood cells. *Early Human Development, 42*, 85–95. https://doi.org/10.1016/0378-3782(95)01626-E

34. Midgley, P. C., Russell, K., Oates, N., *et al.* (1996). Adrenal zone function persists until term in premature infants. *Endocrine Research, 22*, 729–733. https://doi.org/10.1080/07435809609043769

35. Doerr, H. G., Sippell, W. G., Versmold, H. T., *et al.* (1988). Plasma mineralocorticoids, glucocorticoids, and progestins in preterm infants: A longitudinal study during the first week of life. *Pediatric Research, 23*, 525–529. https://doi.org/10.1203/00006450-198805000-00018

36. Scott, S. M., & Watterberg, K. L. (1995). Effects of gestational age, postnatal age, and illness on plasma cortisol concentrations in preterm infants. *Pediatric Research, 37*, 112–116. https://doi.org/10.1203/00006450-199501000-00021

37. De Leon, D. D., & Stanley, C. A. (2007). Mechanisms of disease: Advances in the diagnosis and treatment of hyperinsulinism in the newborn. *Nature Clinical Practice Endocrinology & Metabolism, 3*, 57–68. https://doi.org/10.1038/ncpendmet0368

38. Cornblath, M., Hawdon, J. M., Williams, A. F., *et al.* (2000). Controversy over the definition of neonatal hypoglycemia: Suggested operational thresholds. *Pediatrics, 105*, 1141–1145. https://doi.org/10.1542/peds.105.5.1141

39. Carmen, S. (1986). Neonatal hypoglycemia in response to maternal glucose infusion before delivery. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 15*, 319–323. https://doi.org/10.1111/j.1552-6909.1986.tb01403.x

40. Collins, J. E., & Leonard, J. V. (1984). Hyperinsulinism in hypoglycemic and low-birth-weight infants. *The Lancet, 2*, 311–313. https://doi.org/10.1016/S0140-6736(84)92685-0

41. Whipple, A. O., & Franz, V. K. (1935). Islet cell adenoma with hyperinsulinism: A review. *Annals of Surgery, 101*, 1299–1335. https://doi.org/10.1097/00000658-193506000-00001

42. Wackernagel, D., Dube, M., Blennow, M., *et al.* (2016). Continuous subcutaneous glucose monitoring is accurate in term and near-term infants at risk of hypoglycemia. *Acta Paediatrica, 105*, 917–923. https://doi.org/10.1111/apa.13479

43. Sprague, J. E., & Arbelaez, A. M. (2011). Glucose hypoglycemia: Mechanisms and counterregulatory responses. *Pediatric Endocrinology Reviews, 9*, 463–473.

44. Adamkin, D. H. (2016). Neonatal hypoglycemia. *Current Opinion in Pediatrics, 28*, 150–155. https://doi.org/10.1097/MOP.0000000000000319

45. Rozance, P. J., & Hay, W. W. Jr. (2016). New approaches to the management of neonatal hypoglycemia. *Maternal Health, Neonatology and Perinatology, 2*, 3. https://doi.org/10.1186/s40748-016-0031-z

46. Marles, S. L., & Casiro, O. G. (1998). Persistent neonatal hypoglycemia: Diagnosis and treatment. *Paediatrics & Child Health, 3*, 16–19. https://doi.org/10.1093/pch/3.1.16

47. Beardsall, K., Vanhaesebrouck, S., Ogilvy-Stuart, A. L., *et al.* (2013). Evaluation of a continuous glucose monitoring sensor in preterm infants. *Archives of Disease in Childhood: Fetal and Neonatal Edition, 98*, F136–F140. https://doi.org/10.1136/archdischild-2012-301661

48. McGowan, J. E., & Perlman, J. M. (2006). Glucose management during and after intensive care in the delivery room. *Clinics in Perinatology, 33*, 183–196. https://doi.org/10.1016/j.clp.2005.11.007

49. Belik, J., Musey, J., & Trussell, R. A. (2001). Continuous glucagon infusion causes severe hyponatremia and thrombocytopenia in a premature infant. *Pediatrics, 107*, 595–597. https://doi.org/10.1542/peds.107.3.595

50. Bhowmick, S. K., & Lewandowski, C. (1989). Prolonged hyperinsulinism and hypoglycemia in asphyxiated, small-for-gestation infants: Case report and review of the literature. *Clinical Pediatrics, 28*, 575–578. https://doi.org/10.1177/000992288902801205

51. Lindley, K. J., Dunne, M. J., Kane, C., *et al.* (1996). Ionic control of beta-cell function in nesidioblastosis: A possible therapeutic role for calcium channel blockade. *Archives of Disease in Childhood, 74*, 373–378. https://doi.org/10.1136/adc.74.5.373

52. Wasserman, D. H., Spalding, J. A., Lacy, D. B., *et al.* (1989). Glucagon is a major regulator of hepatic glycogenolysis and gluconeogenesis during muscle activity. *American Journal of Physiology, 257*, E108–E117.

53. Carter, P. E., Lloyd, D. J., & Duffty, P. (1988). Glucagon for hypoglycemia in small-for-gestational-age infants. *Archives of Disease in Childhood, 63*, 1264–1266. https://doi.org/10.1136/adc.63.10.1264

54. McMahon, A. W., Wharton, G. T., Thornton, P., *et al.* (2017). Use and safety of octreotide in infants with hyperinsulinism. *Pharmacoepidemiology and Drug Safety, 26*, 26–31. https://doi.org/10.1002/pds.4144

55. Virgili, N., Mancera, P., Wappenhans, B., *et al.* (2013). The K(ATP) channel opener diazoxide prevents neurodegeneration: A novel mechanism through activation of the antioxidant pathway. *PLoS ONE, 8*, e75189. https://doi.org/10.1371/journal.pone.0075189

56. Touati, G., Poggi-Travert, F., Ogier de Baulni, H., *et al.* (1998). Long-term treatment of persistent hyperinsulinemic hypoglycemia in infants with diazoxide: A retrospective review of 77 cases and analysis of criteria for predicting efficacy. *European Journal of Pediatrics, 157*, 628–633. https://doi.org/10.1007/s004310050900

57. Durmaz, E., Flanagan, S. E., Parlak, M., *et al.* (2014). Combination of nifedipine and octreotide treatment in hyperinsulinemic hypoglycemic infants. *Journal of Clinical Research in Pediatric Endocrinology, 6*, 119–121. https://doi.org/10.4274/jcrpe.1230

58. Baş, F., Darendeliler, F., & Demirkol, D. (1999). Successful therapy with calcium channel blocker (nifedipine) in persistent hyperinsulinemic hypoglycemia in newborns. *Journal of Pediatric Endocrinology & Metabolism, 12*, 873–878. https://doi.org/10.1515/JPEM.1999.12.6.873

59. Weston, P. J., Harris, D. L., & Harding, J. E. (2017). Dextrose gel treatment does not impair subsequent feeding. *Archives of Disease in Childhood: Fetal and Neonatal Edition.* Advance online publication. https://doi.org/10.1136/archdischild-2016-311396

60. Ter, M., Halibulla, I., Leung, L., *et al.* (2017). Use of dextrose gel in the treatment of neonatal hypoglycemia. *Journal of Paediatrics and Child Health, 53*, 408–411. https://doi.org/10.1111/jpc.13409

61. Rawat, M., Chandrasekharan, P., Turkovich, S., *et al.* (2016). Oral dextrose gel reduces the need for intravenous dextrose therapy in neonatal hypoglycemia. *Biomed Hub, 1*, 448511. https://doi.org/10.1159/000448511

62. Hegarty, J. E., Harding, J. E., Gamble, G. D., *et al.* (2016). Prophylactic oral dextrose gel for newborns at risk of neonatal hypoglycemia: A randomized controlled dose-finding trial (pre-hPOD study). *PLoS Medicine, 13*, e1002155. https://doi.org/10.1371/journal.pmed.1002155

63. Harris, D. L., Alsweiler, J. M., Ansell, J. M., *et al.* (2016). Outcome two years after dextrose gel treatment for neonatal hypoglycemia: Follow-up of a randomized trial. *Journal of Pediatrics, 170*, 54–59.e1. https://doi.org/10.1016/j.jpeds.2015.10.066

64. Harris, D. L., Weston, P. J., Signal, M., *et al.* (2013). Dextrose gel for neonatal hypoglycemia (Sugar Babies Study): A randomized, double-blind, placebo-controlled trial. *The Lancet, 382*, 2077–2083. https://doi.org/10.1016/S0140-6736(13)61645-1

65. Vannucci, R. C., & Vannucci, S. J. (2001). Hypoglycemic brain injury. *Seminars in Neonatology, 6*, 147–155. https://doi.org/10.1053/siny.2001.0044