Glucose Homeostasis in Newborns: An Endocrinology Perspective

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Education Gap

Significant advances have been made in our understanding of the hormonal regulation of glucose homeostasis immediately after birth; however, controversies remain over the definition of clinically significant neonatal hypoglycemia, and interpretation of hormone concentrations in asymptomatic neonates with hypoglycemia.

Abstract

Physiologic adaptations in the postnatal period, along with gradual establishment of enteral feeding, help maintain plasma glucose concentrations in the neonatal period. The definition of normal plasma glucose in the neonatal period has been a subject of debate because of a lack of evidence linking a set plasma or blood glucose concentration to clinical symptoms or predictors of short- and long-term outcomes. However, there is consensus that maintaining plasma glucose in the normal range for age is important to prevent immediate and long-term neurodevelopmental consequences of hypoglycemia or hyperglycemia. The specific management strategy for abnormal glucose levels in neonates depends on the underlying etiology, and interventions could include nutritional changes, medications, hormone therapy, or even surgery. Here, we will review the physiological processes that help maintain plasma glucose in newborns and discuss the approach to a newborn with disordered glucose homeostasis, with an emphasis on the endocrine basis of abnormal glucose homeostasis.

Objectives After completing this article, readers should be able to:

1. Describe the physiology of glucose homeostasis in neonates immediately after birth.
2. Recognize that hypoglycemia during the first 24 to 48 hours after birth is nonketotic.

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ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ATP	adenosine triphosphate
CNS	central nervous system
DEND	developmental delay, epilepsy, and neonatal diabetes
FFA	free fatty acid
GCK	glucokinase
GDH	glutamate dehydrogenase
GH	growth hormone
GIR	glucose infusion rate
HI/HA	hyperinsulinism/ hyperammonemia
IGF-1	insulinlike growth factor 1
IGFBP-3	IGF-binding protein 3
IUGR	intrauterine growth restriction
LGA	large for gestational age
NDM	neonatal diabetes mellitus
PES	Pediatric Endocrine Society
PG	plasma glucose
PNDM	permanent neonatal diabetes mellitus
SCHAD	short-chain L-3-hydroxyacyl-CoA dehydrogenase
SGA	small for gestational age
TCA	tricarboxylic acid
TNDM	transient neonatal diabetes mellitus
VLBW	very low birthweight

3. Appreciate the counterregulatory hormonal responses to declining plasma glucose concentrations in healthy neonates after the transitional period.
4. Explain the steps and the role of the K-ATP channel in insulin secretion.
5. Describe the most common endocrine etiologies of neonatal hypoglycemia.
6. Recognize the risk factors for neonatal hyperglycemia.

INTRODUCTION

The definition of normal plasma glucose in the newborn period has been a subject of ongoing debate (1) because of a lack of evidence linking a set plasma glucose (PG) or blood glucose concentration to clinical symptoms or predictors of short- and long-term outcomes. PG levels are lower in the first 48 hours after birth. In healthy term newborns with no risk factors for hypoglycemia, the PG level correlates positively with postnatal age and birthweight on day 0, (2) and breastfed babies have lower PG concentrations compared with formula-fed babies. (3)(4) Although there is no consensus on the PG concentration cutoffs in the first 2 days after birth among neonatologists and endocrinologists, the Pediatric Endocrine Society (PES) recommends a preprandial cutoff PG concentration of less than 50 mg/dL (2.8 mmol/L) for treatment in all neonates regardless of the presence of risk factors within the first 48 hours. (3) Beyond the transition period of 48 to 72 hours after birth, neonates can maintain PG levels similar to those in older children and adults. (3) Here, we will review the physiological processes that help maintain PG levels in newborns and discuss the treatment approach for a newborn with disordered glucose homeostasis, with an emphasis on the endocrine basis of abnormal glucose homeostasis.

PHYSIOLOGY OF GLUCOSE HOMEOSTASIS IN THE NEWBORN

During pregnancy, the fetus is dependent on the mother for a constant supply of glucose. The relationship between maternal and fetal PG concentrations is linear in mid and late gestation, (5) with minimal difference in their PG levels. However, maternal insulin does not cross the placenta and the fetus makes its own insulin to maintain blood glucose levels. (6) Both in utero and in postnatal life, insulin secretion from the beta cells is tightly linked to PG concentrations. Uptake of glucose into the beta cells via a unique glucose transporter (GLUT2) is the initial step in the insulin secretory process. Once in the cytoplasm, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase (GCK). Further metabolism of glucose through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation results in generation of adenosine triphosphate (ATP). Insulin secretion also occurs in response to other nutrients such as free fatty acids (FFAs) and amino acids. (7)(8) Leucine, alanine, and glutamine can undergo metabolism via α-ketoglutarate and oxaloacetate through the TCA cycle and generate ATP. (9) Increased ratio of ATP to adenosine diphosphate causes closure of K-ATP channels, a type of potassium channel composed of SUR and Kir6.2 subunits, on the beta cell membrane. Closure of K-ATP channels results in depolarization of the beta cell, which then triggers the activation of the voltage-gated calcium channels followed by calcium influx. An increase in the intracellular calcium concentration stimulates insulin release via exocytosis. (10) Metabolic actions of insulin include an increase in cellular glucose uptake, deposition of glucose as glycogen, lipogenesis in adipose tissue, and inhibition of breakdown of triglycerides (lipolysis) and fatty acids (ketone body formation or ketogenesis). Importantly, insulin is also a major fetal growth factor.

With cord clamping at birth, the steady source of glucose from the mother to the infant is abruptly interrupted. In the early hours after birth, until enteral intake is established, the maintenance of PG levels is dependent on the activation of glycogenolysis (breakdown of stored glycogen). Other mechanisms that can provide fuel sources, such as gluconeogenesis (formation of new glucose from noncarbohydrate sources) or ketogenesis, are not established at birth. The levels of glucagon and epinephrine increase after birth, and these hormones mobilize glucose through glycogenolysis. (11) This, along with suppressed insulin levels, maintains lower but stable PG concentrations in the first 4 to 48 hours after birth. In this period, neonates are hypoketotic. (12) Whether the reduced ketogenesis is because of immaturity

of enzymes, as shown in animal studies, or lower threshold for insulin release in the immediate postnatal period, as demonstrated by studies in isolated islets, remains to be confirmed. (13) Transcription of the gluconeogenic enzymes and ketogenesis are potentially activated 12 to 24 hours after birth in response to fatty acid–rich colostrum and changes in hormonal milieu. (14)

Newborns with low birthweight and intrauterine growth restriction (IUGR) have decreased glycogen stores at birth and, therefore, are at risk for hypoglycemia. (15) These newborns also have low fat stores that further increase their risk for fuel insufficiency. Infants of diabetic mothers, on the other hand, are at risk for hypoglycemia mainly because of the presence of high circulating insulin levels and a delay in glucagon increase. The degree of hyperglycemia and resultant hyperinsulinemia in the fetus are a direct reflection of the metabolic control of diabetes in the pregnant woman, with poorly controlled diabetes resulting in macrosomia. (16) With the establishment of feeding, PG levels gradually increase in most neonates and reach levels found in older children and adults by 48 to 72 hours after birth. (3)

The dynamic interplay between nutrient availability and hormones, such as insulin and other counterregulatory hormones, helps maintain normoglycemia in fed and fasting states. A low PG concentration triggers a complex, well-coordinated, and step-wise neuroendocrine response to counteract hypoglycemia. When the PG concentration drops below 80 to 85 mg/dL (4.4–4.7 mmol/L), still within the physiological range, the first response is to shut off insulin secretion to prevent further decrease in glucose levels. (17)(18) This response also allows the brain to use available glucose in the circulation because glucose can easily pass through the blood-brain barrier in an insulin-independent manner. Furthermore, the decrease in insulin removes the inhibitory effect on lipolysis and ketogenesis, thereby providing alternative fuel sources. (3)(12)(18)

Glucagon, growth hormone (GH), catecholamines, and cortisol are counterregulatory hormones that help mobilize stored glucose and provide alternative fuel sources for energy. Hepatic glycogen serves as the first and immediate source of glucose. With a decrease in PG levels, the increase in glucagon and epinephrine levels promotes hepatic glycogenolysis and provides a source of glucose for a few hours. (19) Epinephrine also inhibits insulin secretion and stimulates glucagon release from the pancreatic islets. Epinephrine and GH promote lipolysis to provide FFAs, which serve as an energy source for skeletal and cardiac muscle. Further β-oxidation of fatty acids (mediated through actions of epinephrine and glucagon) results in the formation of ketone bodies, an alternative energy source for the brain. A continuing decline in glucose concentrations stimulates secretion of other counterregulatory hormones, namely cortisol and GH. Cortisol, along with epinephrine, increases gluconeogenesis from noncarbohydrate sources such as alanine, lactate, and glycerol. Cortisol and GH produce gluconeogenic substrates alanine and glycerol through muscle breakdown and lipolysis, respectively. Also, cortisol increases the transcription of enzymes involved in gluconeogenesis. The purpose of these complex systems is to maintain PG within age-appropriate physiologic ranges and to avoid hypoglycemia-related negative outcomes. The hormonal responses to hypoglycemia are summarized in Fig 1.

Glucose is the primary energy source for the central nervous system (CNS). However, the CNS can use alternative fuel sources, such as ketone bodies and lactate, for a limited duration when glucose is scarce. Because the brain is large compared with the rest of the body in the newborn, the glucose needs of a newborn are significantly higher than those of older children and adults. Newborns need a glucose infusion rate (GIR) of 4 to 6 mg/kg per minute compared with adults who need 1 to 2 mg/kg per minute to maintain PG levels within the normal range. The brains of newborns are also more susceptible to the deleterious effects of low PG levels.

HYPOGLYCEMIA IN THE NEWBORN

Neonates born small or large for gestational age (SGA or LGA), infants of diabetic mothers, and preterm infants are at risk for transient hypoglycemia. Screening for hypoglycemia is the standard of care for these newborns. The incidence of neonatal hypoglycemia during the transition period among at-risk infants varies depending on the cutoff chosen to identify hypoglycemia, the timing of screening in relation to feeding, and the laboratory method used to measure the blood glucose or PG. For instance, Harris et al (4) used a cutoff of less than 47 mg/dL (2.6 mmol/L) and reported an incidence of 51%, whereas Stark et al (20) used a lower cutoff—less than 40 mg/dL (2.2 mmol/L)—and found a 27% incidence in the at-risk group regardless of the age of the infant. The 2015 PES guideline on neonatal hypoglycemia recommends maintaining preprandial PG concentrations above 50 mg/dL (2.8 mmol/L) in the first 48 hours after birth in high-risk neonates without a suspected hypoglycemia disorder. (3) Screening is crucial to identify and treat hypoglycemia promptly, because a growing body of evidence has shown a significant association between neonatal hypoglycemia and long-term negative neurodevelopmental outcomes. (21)(22) McKinlay and

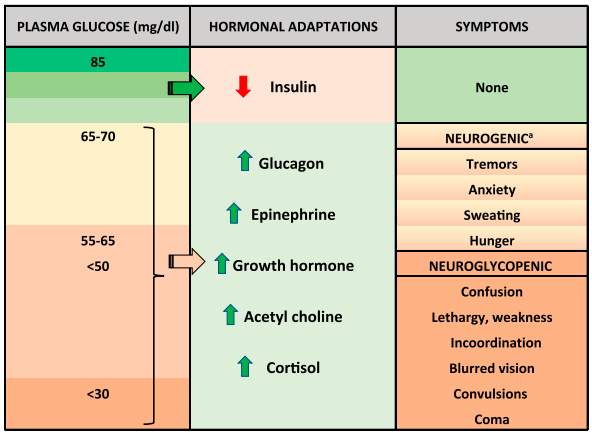

Figure 1. Hormonal responses to hypoglycemia. [a]Symptoms mediated through sympathoadrenal and parasympathetic responses.

colleagues reported a negative association between the duration of blood sugar concentrations outside the arbitrary 54 to 72 mg/dL (3–4 mmol/L) range during the first 48 hours after birth and neurodevelopmental outcomes at 2 years of age. (22) Also, in the same cohort, worse executive and visual-motor integration were noted in children who had more severe and frequent periods of neonatal hypoglycemia at 4.5 years of age. (21)(22)

A healthy newborn is expected to maintain PG concentrations at or above 60 mg/dL (3.3 mmol/L) after 48 hours of age. (3) Although recurrent hypoglycemia is a common metabolic problem in neonates, recognizing neonates at risk for a persistent hypoglycemia disorder is not as straightforward because most neonates are asymptomatic or exhibit nonspecific symptoms. There is no pathognomonic sign or symptom for hypoglycemia. Most of the common symptoms and signs are nonspecific, and include abnormal cry, decreased feeding, jitteriness, irritability, pallor, cyanosis, hypothermia, or diaphoresis. In severe cases, neonates may present with lethargy, tachypnea, hemodynamic instability, apnea, seizures, or even cardiac arrest. (23) A high index of suspicion for a hypoglycemia disorder should be maintained to identify true pathologies and establish appropriate treatment. Though the presence of symptoms or signs of hypoglycemia has been suggested to determine treatment thresholds, current clinical practice is to treat the hypoglycemia without any delay even in the absence of symptoms.

Etiology of Hypoglycemia

A well-coordinated, dynamic balance among intake (feeding), tissue use (glucose uptake, glycolysis, glycogen synthesis), and endogenous production (gluconeogenesis, glycogenolysis) of glucose is necessary to maintain euglycemia. Therefore, a diminished exogenous or endogenous supply, or increased utilization of glucose can cause hypoglycemia. Hypoglycemia can be classified as transient or permanent, but there is no consensus regarding the duration of the hypoglycemia to differentiate one form from the other. Transient hypoglycemia typically resolves within the first few days to weeks.

When hypoglycemia persists beyond the first 48 hours, and hypoglycemia arising from maternal diabetes (the most common type of transient neonatal hypoglycemia) and other common etiologies (SGA, LGA, IUGR) are deemed unlikely, there is a higher risk for permanent pathology. Clinically, permanent hypoglycemia usually has genetic causes. The differential diagnosis of persistent hypoglycemia varies and includes endocrine causes (eg, hyperinsulinemia, GH deficiency, hypocortisolism), as well as nonendocrine causes (eg, inborn errors of metabolism). (24) The causes of neonatal hypoglycemia are listed in Table 1. The timing of hypoglycemia in relation to feedings can provide a clue to the etiology. For instance, postprandial hypoglycemia could be due to dumping syndrome or inborn errors of metabolism, whereas fasting or postabsorptive hypoglycemia is due to hyperinsulinism (HI), defects in glycogenolysis or gluconeogenesis enzymes, or counterregulatory hormonal insufficiency. (24)(25) Because neonates and young infants are fed frequently, hypoglycemia may not occur until after the time between consecutive feedings is spaced out long enough.

Hyperinsulinism. Congenital HI is the most common cause of persistent nonketotic hypoglycemia in the newborn and results from dysregulated insulin secretion. HI could be acquired or inherited, and it can be transient or permanent. Initial biochemical tests cannot distinguish the different forms or types of HI. Demonstrating an elevated insulin concentration along with suppressed plasma ketones and FFAs, and a positive response to a glucagon challenge (ie, an increase in PG concentration over 30 mg/dL [1.6 mmol/L] above baseline) at the time of the hypoglycemia is generally enough to establish the diagnosis of HI. (26)(27) In some cases, the insulin level may be inappropriately normal (instead of low) despite a low PG level; therefore, the term *hyperinsulinism* is preferred over *hyperinsulinemia*. (26)(27) Once the diagnosis of HI is established, a trial of diazoxide, a drug that stabilizes the K-ATP channel in the open state, should be attempted as the first-line medical therapy. The success or failure of the diazoxide trial depends on the extent of preservation of K-ATP channel function. This approach has diagnostic value and may guide future evaluations.

Stress-induced "transient HI" is an acquired cause of persistent hypoglycemia (despite its name) and is usually associated with birth asphyxia, IUGR/SGA infants, and preeclampsia. (27)(28) The exact pathophysiology is not well understood. It can last several days to weeks after birth; however, some reports show that the course can rarely be prolonged up to a year. (27) Diazoxide is usually effective in the treatment of perinatal stress-induced HI. (29)

The incidence of inherited HI is estimated to be 1 in 50,000 live births; however, it can be diagnosed more often in areas with higher rates of consanguineous marriages. (30) Affected newborns are usually born LGA because of chronic intrauterine exposure to elevated insulin, a fetal growth factor, and present with fasting and postprandial hypoglycemia. (31) HI could be secondary to channelopathies (*ABBC8, KCNJ11*), enzyme anomalies (GCK, glutamate dehydrogenase [GDH], short-chain L-3-hydroxyacyl-CoA dehydrogenase [SCHAD]), or defects in a transcription factor (*HNF4A*). (30) Pathologically, the lesion could be focal or diffuse. Inactivating mutations of the *ABCC8* and *KNCJ11* as the cause of HI are estimated to account for 60% of all identifiable mutations, including the majority (85%) of focal or diffuse diazoxide unresponsive forms. (31)(32) Activating mutations of GCK also result in diazoxide unresponsive HI. (33)

HI resulting from dominant activating mutations of GDH, encoded by *GLUD1*, is a common form of diazoxide-responsive HI. (33) A mild, persistently elevated plasma ammonia level independent of glucose levels is characteristic. This condition is also known as hyperinsulinism/hyperammonemia (HI/HA) syndrome. Leucine, a branch-chained amino acid, directly regulates insulin secretion independent of glucose by allosteric activation of GDH. (34) Affected individuals with HI/HA syndrome have increased sensitivity to leucine-stimulated insulin release. Another rare type of diazoxide-responsive HI occurs because of impaired SCHAD (encoded by *HADH*) activity that leads to disinhibition of GDH. (35) Elevated 3-hydroxybutyryl-carnitine, a metabolite that is routinely screened through the newborn screening programs in some states, is a unique laboratory finding in SCHAD-HI. (33)(36) Ammonia levels are normal in this form. (37) There are a few other but rarer forms of congenital HI, as described elsewhere in the literature. (32)(33)

Hypocortisolism. Adrenal insufficiency, primary or secondary, is a rare cause of persistent neonatal hypoglycemia. Cortisol is one of the key counterregulatory hormones and contributes to glucose homeostasis through enhancement of gluconeogenesis. Cortisol deficiency can lead to hypoglycemia, particularly when enteral feeding is delayed or not adequately established. There is no

TABLE 1. **Etiologies of Neonatal Hypoglycemia**

TRANSIENT	PERSISTENT
Endocrine Causes	

• HI
• Infant of diabetic mother
	• HI
	  • Transient[a] (perinatal stress-HI)
	  • Permanent
	  • Channelopathies
	  • Activating GLUD1 mutations
	  • SCHAD deficiency
	  • Other rare genetic HI
	• Panhypopituitarism
	• Isolated GH deficiency
	• Adrenal insufficiency (primary or secondary)

Nonendocrine Causes	

• Delayed enteral feeding
• Prematurity
• IUGR/SGA
• Sepsis
• Maternal use of β-blockers
• Polycythemia
	• Inborn errors of metabolism
	  • Galactosemia
	  • Glycogen storage disease
	  • Gluconeogenic disorders
	  • Fatty acid oxidation disorders
	  • Organic acidurias
	• Hepatic dysfunction

GH=growth hormone; GLUD=glutamate dehydrogenase; HI=hyperinsulinism; IUGR=intrauterine growth restriction; SCHAD=short-chain L-3-hydroxyacyl-CoA dehydrogenase; SGA=small for gestational age.

[a]*Current nomenclature for this type of hypoglycemia, which may, however, last for several weeks or months.*

consensus regarding normal values of cortisol and adrenocorticotropic hormone (ACTH) within the first few weeks of age. Low cortisol levels are often observed in neonates, and are possibly caused by immaturity of the hypothalamus-pituitary-adrenal axis and underdeveloped circadian rhythm. (38) Cortisol deficiency should be suspected as the cause of persistent hypoglycemia in neonates with midline defects such as holoprosencephaly or septo-optic dysplasia. In such circumstances, cortisol deficiency is usually a component of panhypopituitarism. As such, other pituitary hormone concentrations should be assessed, and appropriate treatment should be initiated as applicable. A low cortisol level at the time of hypoglycemia has poor specificity for the diagnosis of adrenal insufficiency. (39) An ACTH stimulation test will help diagnose adrenal insufficiency and distinguish primary versus secondary causes of hypocortisolism.

GH Deficiency. GH is another counterregulatory hormone that is secreted from the anterior pituitary. GH stimulates lipolysis, providing fatty acids and ketone bodies as alternative fuel sources. GH deficiency can be isolated, but it is mostly present as part of panhypopituitarism, especially when the infant is born with a midline defect. GH, cortisol, and thyroxine regulate bilirubin metabolism; therefore, prolonged jaundice, especially when associated with hypoglycemia, may be a sign of panhypopituitarism. (40) A low GH level at the time of hypoglycemia has poor specificity for the diagnosis of GH deficiency in older children. (39) However, GH levels are elevated in neonates regardless of hypoglycemia. Although a low GH level cannot prove deficiency, a random GH concentration of at least 10 to 15 ng/mL (10–15 μg/L) is considered adequate within the first month after birth. (41) Repeated measurements of GH levels should be performed (regardless of the glycemic level) to increase diagnostic value. Provocative tests are rarely indicated in the newborn period. Insulinlike growth factor 1 (IGF1) and IGF-binding protein 3 (IGFBP3) are produced in the liver as a function of GH, and are sensitive markers of circulating GH concentration. The plasma IGF1 level is directly affected by the nutritional status; therefore, it could be falsely low in IUGR/SGA neonates. The plasma IGFBP3 concentration, on the other hand, is more stable and is not affected by the nutritional status. (42) Concomitant measurement of these growth factors may aid in the diagnosis of GH deficiency.

Physical Examination

A thorough physical examination should be performed in all newborns with hypoglycemia regardless of the presence of known risk factors for hypoglycemia. This practice will help guide the diagnostic evaluation, thereby shortening the time to an accurate diagnosis and initiation of appropriate treatment. The diagnosis of LGA may be a sign of exposure to high concentrations of insulin in utero as is the case in infants of diabetic mothers or those born with congenital HI. (43)(44) A diagnosis of SGA may indicate perinatal stress, a well-described condition associated with transient HI. (27) Midline defects or brain malformations (eg, holoprosencephaly) may suggest a pituitary hormone (eg, GH, ACTH) deficiency, either isolated or combined. (45) Infants with hypoglycemia and nystagmus may have septo-optic dysplasia, a well-known midline brain anomaly that is highly associated with hypopituitarism. Presence of syndromic overgrowth conditions (macrocrania and gigantism in Sotos syndrome, hemihypertrophy and macroglossia in Beckwith-Wiedemann syndrome) in a newborn with hypoglycemia may suggest hyperinsulinism. (46)

Laboratory Evaluation

Screening for hypoglycemia is generally done via point-of-care handheld glucometers. These devices use glucose oxidase as a reducing agent and measure capillary blood sugar in a matter of seconds. The capillary blood sugar concentration measured by glucose meters may be 11% lower than the PG level. (47) Therefore, a low glucometer reading should always be verified with PG estimations to avoid misinterpretation of the "critical sample" results. Continuous glucose monitors are widely used in patients with type 1 diabetes, but they have gained attention for use in newborns only recently. They measure glucose concentration in the interstitial fluid, which generally correlates well with PG concentrations; however, hemodynamic instabilities, including thermoregulation problems due to comorbid situations or prematurity, can potentially affect the reliability of the data. Continuous glucose monitoring cannot be a substitute for PG measurements for the diagnosis of hypoglycemia, and currently the evidence to suggest routine clinical use is insufficient. (47)(48)

An infant's history or physical examination findings may guide prioritization of some tests over others, but a considerable percentage of affected neonates usually do not have any identifiable risk factors or physical examination findings. Considering the limitations in daily blood draw volumes and the prevalence of different etiologies, it is reasonable to take a tiered approach (Fig 2). Most endocrinologists recommend obtaining the following blood tests (critical

sample) as first tier during a confirmed hypoglycemic episode (ie, PG concentration <50 mg/dL [2.8 mmol/L]) to rule out endocrine etiologies: electrolytes, bicarbonate, insulin, β-hydroxybutyrate, FFAs, cortisol, GH, and lactate. A controlled fasting may be needed to induce hypoglycemia if the neonate does not develop hypoglycemia during a frequent feeding schedule. Further evaluation, including measurement of serum amino acid or acyl carnitine profiles, urine organic acid profile, advanced tests for cortisol or GH deficiency, and testing for genetic disorders of hyperinsulinism, will be guided based on clinical course, associated features, and the results of the critical sample (Fig 2). Recent advances in molecular genetics have enabled providers to identify the underlying pathology in the insulin secretory process precisely. Many commercial laboratories offer a congenital HI panel including the most commonly implicated genes: *ABCC8* (SUR1), *KCNJ11* (Kir6.2), *GCK (glucokinase)*, *GLUD1* (GDH), *HADH* (SCHAD), and others. (31)(32)(33)

Management of Hypoglycemia

The goal in the management of neonatal hypoglycemia is to restore PG levels to a safe, age-appropriate range. The symptoms of the affected neonate will determine the route of treatment, enteral versus parenteral, to achieve the desired goal.

Enteral Feeding. Decreased substrate availability, as in the case of delayed enteral feeding, is one of the most common causes for hypoglycemia in all newborns. Enteral feeding should be instituted in all newborns as quickly as possible unless there are contraindications because of other morbidities. Breastfeeding should be encouraged for various health and psychosocial benefits. Breastfed infants were shown to have significantly less recurrent low glucose concentrations compared with formula-fed infants. (23) When hypoglycemia persists on a typical feeding regimen, more frequent feeding regimens or use of calorically dense formulas or fortification of breast milk may be tried.

Recent studies assessed the efficacy of an oral 40% dextrose gel for the treatment or prevention of asymptomatic hypoglycemia in at-risk infants. (49)(50) Harris et al (51) assessed the efficacy of a dextrose gel for the treatment of neonatal hypoglycemia in at-risk neonates. Neonates treated with a dextrose gel (200 mg/kg) had less treatment failure, defined as a blood sugar less than 47 mg/dL (2.6 mmol/L), 30 minutes after the second dose. (51) In addition, the treatment group had less hypoglycemia-related NICU admissions and higher breastfeeding success rates 2 weeks after the hypoglycemia event. (51) Importantly, the groups did not differ with regard to the frequency of neurosensory impairment at the 2-year follow-up. (52) Similar findings of a lack of difference in long-term

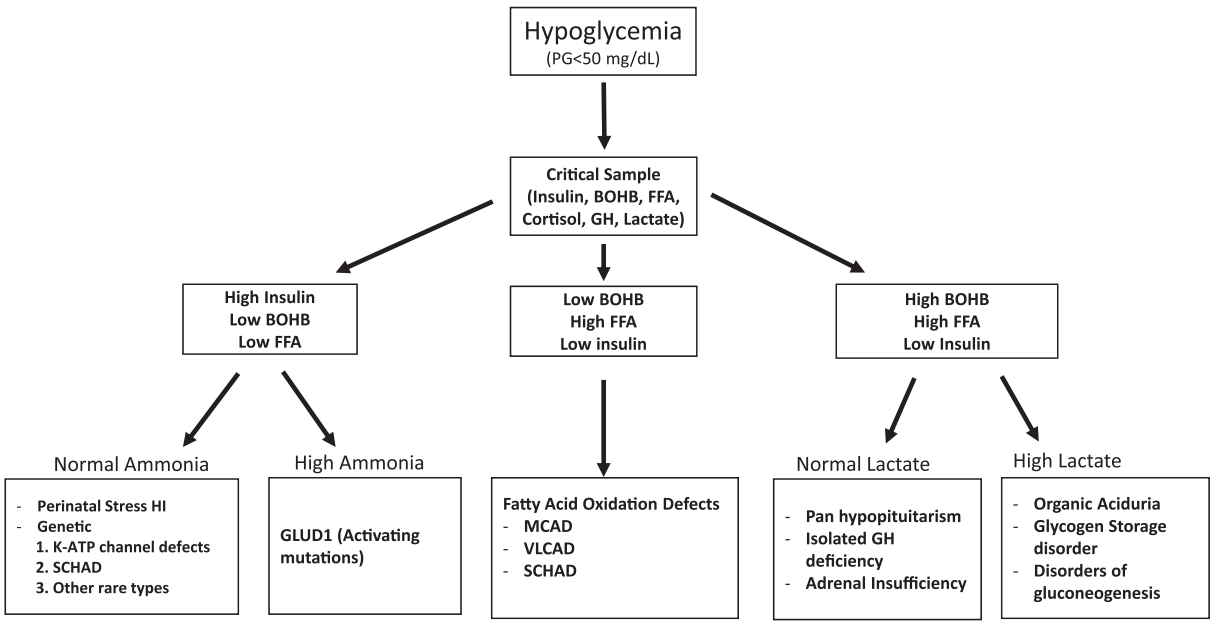

Figure 2. Newborn with persistent hypoglycemia. BOHB=β-hydroxybutyrate; FFA=free fatty acid; GH=growth hormone; GLUD=glutamate dehydrogenase; HI=hyperinsulinism; K-ATP=adenosine triphosphate sensitive potassium channel; MCAD=medium-chain acyl-CoA dehydrogenase; PG=plasma glucose; SCHAD=short-chain L-3-hydroxyacyl-CoA dehydrogenase; VLCAD=very-long-chain acyl-CoA dehydrogenase.

TABLE 2. **Etiology of Hyperglycemia in Newborn**

Very low birthweight	
Sepsis	
Stress	
Steroid therapy	
Parenteral dextrose	
Neonatal Diabetes	**Other Associated Features**
Transient neonatal diabetes	
6q24 duplication	Intrauterine growth restriction
KCNJ11 mutations	
ABCC8 mutations	
ZFP57	Macroglossia, developmental delay
Permanent neonatal diabetes	
Without exocrine pancreas defects	
KCNJ11 mutations	
ABCC8 mutations	
INS gene mutations	
Glucokinase mutations	
With exocrine pancreas insufficiency	
EIK2AK3	Skeletal dysplasia, liver disease
GATA4, *GATA6* mutations	Cardiac defects
PDX1 mutations	
PTF1A	Neurologic abnormalities, kidney disease
With systemic manifestations	
FOXP3 mutations	Immune dysregulation, dermopathy, enteropathy,
Wolframin mutations	Diabetes insipidus, optic atrophy, deafness, cataracts
KCNJ11	DEND syndrome [developmental delay, epilepsy, neonatal diabetes], neurologic defects
GLIS3	Hypothyroidism, kidney cysts, liver fibrosis, glaucoma
NEUROD1	Learning difficulty, deafness, neurologic deficits
NEUROG3	Diarrhea
HNF1beta	Urogenital defects

neurologic outcomes after the use of a glucose gel were reported at 2-year follow-up by Weston et al. (53) Although a dextrose gel appears to be a promising modality for the treatment of asymptomatic hypoglycemia because of its rapid onset of action, availability, and lower cost, there is no evidence to support its superiority to other nutritional approaches including breast milk or formula feeding in preventing hypoglycemia. Hegarty et al did not find the use of a dextrose gel to be efficacious in preventing neonatal hypoglycemia in at-risk neonates. (54)

Intravenous Dextrose. When enteral feeding is contraindicated or the newborn suffers from symptomatic hypoglycemia, intravenous dextrose is the treatment of choice for acute management. The standard approach is to give a 2 mL/kg (200 mg/kg) bolus of 10% dextrose followed by a continuous dextrose infusion to achieve euglycemia (55); however, recent evidence recommends caution when using a dextrose bolus for the treatment of asymptomatic hypoglycemia. The main concern with unnecessary bolus treatment is the potential association of rapid correction of hypoglycemia and wide variability in glucose concentrations with negative neurodevelopmental outcomes. (22) Under normal circumstances, a GIR of 4 to 6 mg/kg per minute is usually sufficient in otherwise healthy full-term infants, whereas premature infants may need higher rates, up to 6 to 8 mg/kg per minute, to maintain euglycemia. The GIR should be titrated up to achieve the desired PG range. Infants with hyperinsulinemia usually require higher GIR (>15 mg/kg per min) compared to those without hyperinsulinemia. Placement of a central venous catheter may be needed to deliver high enough glucose concentrations to stabilize PG levels. When dextrose infusion is not enough, or a prolonged and persistent type of etiology is suspected, pharmacologic treatment will be necessary.

Pharmacologic Options. Diazoxide has historically been the first-line treatment for HI and is the only drug approved by the US Food and Drug Administration for the treatment of HI. Diazoxide keeps the beta cell K-ATP channel open, thereby preventing membrane depolarization, a necessary step for normal insulin secretion. Localization of the defect in the insulin secretory pathway and the type of genetic mutation will determine diazoxide responsiveness. For instance, neonates with recessive mutations of *ABCC8* (encoding SUR1 protein) and *KCNJ11* (encoding Kir6.2 protein) are unresponsive to diazoxide whereas infants with activating mutations of GDH or inactivating mutations of SCHAD are responsive to diazoxide. A typical starting dose for diazoxide is 5 to 10 mg/kg per day divided in 3 doses. It may take up to 2 to 3 days until the full therapeutic effect is seen. The dose is usually titrated up gradually until the desired effect is achieved with a maximum dose of 15 to 20 mg/kg per day; however, close monitoring is necessary for a rare but potentially fatal, dose-dependent side effect of fluid retention and pulmonary hypertension at higher doses. (56) Chlorothiazide may be added to the regimen to counteract fluid retention. Hypoalbuminemia was speculated to increase the risk of diazoxide toxicity because this compound is typically bound to plasma proteins at a high percentage. (57) If diazoxide fails to restore euglycemia after a few days of trial, then octreotide, a long-acting somatostatin analog, may be considered because it directly inhibits the opening of voltage-gated calcium channels which are more distal in the insulin secretory pathway. (44)

Octreotide is used as an off-label treatment for diazoxide-unresponsive HI; however, its use has been linked to necrotizing enterocolitis, particularly in preterm infants. (58) It is usually given as a continuous infusion at a dose 5 to 40 μg/kg per day. (59) Tachyphylaxis may develop after a few days of use, even at escalating doses. Safety and efficacy have not been established in the context of HI treatment in neonates; therefore, octreotide should be used with caution, and every effort should be made to shorten the duration of treatment.

Glucagon. Glucagon should be readily available at the bedside of a neonate who is being treated for hypoglycemia with labile control. In addition to its therapeutic effect, glucagon injection also has a diagnostic value. (26) Glucagon can be given in a continuous infusion as a bridge therapy at a dose of 1 mg/day over 24 hours regardless of the birthweight and gestational age of the neonate. (60) Glucagon is generally well-tolerated; however, rebound hypoglycemia, vomiting, hyponatremia, and a rare skin reaction, erythema necrolyticum migrans, have been reported. (61)(62)(63)

Glucocorticoids. Glucocorticoids hypothetically help with the stabilization of blood sugar via enhancement of gluconeogenesis; however, studies have shown that infants treated with hydrocortisone or dexamethasone alone required additional medical treatment to achieve euglycemia. (61)(64)(65) The potential risks associated with the use of glucocorticoid therapy outweigh the benefits, unless the etiology of hypoglycemia is adrenal insufficiency. The use of glucocorticoids for the treatment of persistent hypoglycemia of unknown etiology is not recommended.

Growth Hormone. GH will stabilize PG levels if the etiology of hypoglycemia is GH deficiency. Screening should be undertaken for other pituitary hormones if the neonate is suspected to have hypoglycemia resulting from GH deficiency or adrenal insufficiency. An endocrinology consultation early in the course of management should be considered.

Surgery. Failure of medical intervention to stabilize PG levels warrants exploration of surgery as an alternative treatment for hypoglycemia. Specialized imaging using [^{18}F]fluoro-L-DOPA positron emission tomography with computed tomography distinguishes focal from diffuse lesions in the pancreas and guides surgical intervention. There are currently only 2 congenital HI centers (Congenital Hyperinsulinism Center at the Children's Hospital of Philadelphia, Philadelphia, PA and Cook Children's Hyperinsulinism

Center, Fort Worth, TX) in the United States where advanced imaging and precision surgery can be performed, including removal of a focal lesion or near total pancreatectomy.

When is a Newborn with a History of Hypoglycemia Safe for Discharge?

The 2015 PES recommendations state that a preprandial PG level of at least 60 mg/dL (3.3 mmol/L) is within the safe range for discharge for most infants; but a concentration of 70 mg/dL or higher (≥3.9 mmol/L) is recommended if a persistent hypoglycemia disorder is suspected, or if the infant is receiving pharmacologic treatment for hypoglycemia. (3) A safety fast should always be done to determine whether the neonate could be safely discharged from the hospital. Duration of a safety fast is typically 6 to 8 hours in the first month after birth, which can be conducted by skipping a mealtime feeding while closely monitoring the blood sugar until the test is complete. The infant's blood sugar level should remain above 60 mg/dL ([3.3 mmol/L] or 70 mg/dL [3.9 mmol/L] if any medication treatment has begun or the patient is suspected to have hypoglycemia with a permanent etiology) before the infant is considered safe to be discharged.

HYPERGLYCEMIA

In a term newborn, hyperglycemia is a much less common clinical problem than hypoglycemia. However, it is a common metabolic abnormality in low-birthweight, preterm, and critically ill newborns. (23) The definition of hyperglycemia in newborns varies, with the most accepted being any PG concentration greater than 125 mg/dL (6.9 mmol/L). However, studies examining consequences of hyperglycemia or treatment thresholds have used varying and higher glucose thresholds. For instance, Zamir et al set levels more than 180 mg/dL (10 mmol/L) as the threshold for hyperglycemia when evaluating consequences, and Lemelman et al recommend treatment with insulin if glucose levels are above 250 mg/dL (13.8 mmol/L). (66)(67)

It is important to recognize and manage hyperglycemia in newborns as it could have significant consequences. Immediate consequences include dehydration, ketosis, diabetic ketoacidosis, poor growth, weight loss, poor perfusion, and susceptibility to infection; (23) long-term consequences include negative effects on neurodevelopmental outcomes. (68)(69) Changes in osmolality and blood flow, endothelial injury, intracellular acidosis, and increased oxidative stress have been implicated in hyperglycemia-mediated injury and its consequences. (70)

Etiology of Hyperglycemia

Risk factors for hyperglycemia in preterm and very-low-birthweight (VLBW) infants include critical illness, infection, stress, medications, parenteral glucose administration, and inadequate pancreatic insulin production. (71) Infections, sepsis, and stress lead to release of cytokines and stress hormones that decrease peripheral glucose utilization as well as increase gluconeogenesis, thereby contributing to hyperglycemia. (23)(70) When glucose levels are persistently greater than 250 mg/dL (13.8 mmol/L) in the absence of identifiable causes, and persist beyond 7 to 10 days of age, neonatal diabetes mellitus (NDM) should be considered. (66)

NDM is rare and estimated to affect 1 in 90,000 to 160,000 live births. (66) By definition, NDM is diabetes diagnosed by 12 months of age, though most infants are diagnosed by 6 months of age. It can result from a range of defects in the beta cells that affect normal development, glucose sensing, metabolism, insulin synthesis, insulin secretion, or enhance beta cell apoptosis. The etiology of NDM is most often monogenic, especially in term infants. Preterm infants could also have a monogenic etiology for their diabetes (31% of cases) and tend to present at an earlier age than full-term infants. (72) NDM could be transient (TNDM) or permanent (PNDM).

Infants with TNDM present earlier on average compared with infants with the permanent form of NDM and outgrow their need for insulin by 3 to 18 months of age. (73) Diabetes may recur at puberty, pregnancy, or in older age, and in some cases, permanent diabetes mellitus may result. The most common cause of TNDM (70%) is related to the 6q24 region of the chromosome. Normally, 6q24 is only paternally expressed. TNDM occurs when 2 copies of this region are expressed due to uniparental disomy, duplication of the paternal allele, or lack of suppression of expression of maternal allele. Other reported features include IUGR, umbilical hernia, macroglossia, deafness, hypotonia, and developmental disabilities. The second most common cause of TNDM (25%) is heterozygous mutations in *ABCC8* or *KCNJ11* (both genes are located in chromosome 11p15.1). Rare causes of TNDM include homozygous or compound heterozygous mutations in transcription factor Zinc Finger protein 57 (gene located in chromosome 6p22.1).

The most common defects leading to PNDM were found in *KCNJ11* and *ABCC8*, genes that encode subunits of the K-ATP channel in the beta cell, accounting for 45% of cases when there is parental consanguinity. (74)(75)(76)(77) KCNJ11 channels are also found in the brain, and therefore children with mutations in *KCNJ11* may have other

neurologic features such as developmental delay, epilepsy, and neonatal diabetes (DEND syndrome). Indeed, neurologic features are the most common extrapancreatic feature in infants with NDM. (74) Insulin gene mutations (*INS1*) account for 10% to 15% of PNDM cases, (78) and do not differ in incidence based on parental consanguinity. (74) Defects in GLUT2 or GCK, leading to impaired or absent sensing of glucose by the beta cell, and mutations of voltage-gated calcium channels can also result in NDM. (79)(80)(81)

Other genes implicated in NDM include genes involved in beta cell health, immunity, and pancreatic development. Beta cell destruction is associated with mutations in *INS, EIF2AK3* (Wolcott-Rallison syndrome), *IER3IP1, FOXP3* (IPEX syndrome), and *WFS1* (Wolfram syndrome). (66) In these instances, the presence of other clinical features points to specific etiologies, though some associated features may appear much later. Specifically, *FOXP3* defects present with immune dysregulation, skin rash, and diarrhea, many of which may be noted later in life. (82) Defects in *WFS-1* (Wolfram syndrome) should be considered in an infant with diabetes, deafness, and ocular manifestations, though diabetes is usually a later presentation. Generalized defects in the genes involved in pancreatic development such as *PDX1 (IPF1), PTF1A, HNF1B, RFX6, GATA4, GATA6, GLIS3, NEUROG3, NEUROD1, PAX6, NKX2-2,* and *MNX1* can result in exocrine pancreatic insufficiency and neonatal diabetes. (66)

The etiology of hyperglycemia in the newborn is summarized in Table 2.

Diagnosis of Hyperglycemia

Hyperglycemia in the neonate can be insidious and only detected on routine laboratory tests or urinalysis. Infants are at risk for dehydration, acidosis, failure to thrive, and poor weight gain. Symptoms and signs such as tachypnea and desaturations may be seen if there is progression to diabetic ketoacidosis. Rarely, features of altered sensorium or stroke can be seen in response to hyperviscosity and severe hyperglycemia.

The possibility of an infection should be considered in neonates with hyperglycemia, especially preterm and VLBW infants, because hyperglycemia may be a presenting sign of an infection or sepsis. A thorough family history should be elicited in newborns with hyperglycemia and suspected NDM, because the genetic mutations that lead to NDM may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. IUGR and low birthweight are noted in NDM associated with *KCNJ11, ABCC8, 6q24, INS,* and *GCK* mutations.

The physical examination can offer clues to the etiology of diabetes, though some of the features of syndromic diabetes may not become clinically evident until later. In the context of neonatal hyperglycemia, presence of macroglossia and umbilical hernia suggest 6q24-related TNDM; the presence of cardiac defects may point to mutations in *GATA6* or *GATA4*; and the presence of diarrhea may point to exocrine pancreatic insufficiency and mutations in *NeuroG3* or *FOXP3*. Neurologic manifestations may occur in NDM of many genetic etiologies including *KCNJ11* mutations. The finding of skeletal dysplasia along with NDM suggests Wolcott-Rallison syndrome. (83) For a more detailed list of etiologies, we refer the reader to the review on NDM by Lemelman et al. (66)

Management of Hyperglycemia

The initial management of hyperglycemia should include decreasing intravenous dextrose concentrations, correction of dehydration, addressing the underlying conditions that could contribute to stress (eg, hypoxia, acidosis, poor perfusion, infections), and if possible, stopping medications such as steroids or catecholamines that could contribute to hyperglycemia. Increasing the rate of the amino acid infusion could increase protein synthesis, anabolism, and insulin secretion, thereby reducing hyperglycemia. Establishing enteral feedings to augment gut-derived hormones (incretins) and decreasing lipid infusion rates to decrease gluconeogenesis and insulin resistance have also been shown to help correct hyperglycemia. (23)(84)

Hyperglycemia may persist in spite of all the aforementioned interventions, and some preterm neonates may need short-term insulin therapy. Zamir et al reported a lower mortality in extremely preterm infants with hyperglycemia who were treated with insulin (67); however, larger, controlled, prospective studies are needed to validate these observations. Care should be given to prevent hypoglycemia with insulin therapy, because hypoglycemia as well as glucose variability can affect outcomes. (85)

When a diagnosis of NDM is suspected, ultrasonography of the pancreas should be performed to look for developmental defects. Genetic testing for NDM should be performed to confirm the diagnosis and establish the etiology, because therapies vary based on underlying cause. In infants diagnosed with NDM, insulin or sulfonylureas are the main lines of therapy. Mutations in K-ATP channel (*KCNJ11* and *ABCC8* mutations) may respond to sulfonylureas. A trial of sulfonylurea in consultation with endocrinology may be warranted in neonates with NDM even before the genetic diagnosis is confirmed. (86)(87)(88)

Sulfonylurea treatment may ameliorate neurologic outcomes in DEND syndrome. (88)(89) Families with an infant with IPEX syndrome may need counseling, and early stem cell transplantation could be beneficial in these cases. (82)

SUMMARY

Concentrations of PG in the newborn period are maintained in the normal range for age through postnatal adaptations and gradual establishment of enteral feeding. In the event of hypoglycemia, a concerted counterregulatory mechanism coordinates various physiological processes to provide glucose or alternative fuel sources such as ketone bodies, especially to the brain. Maintenance of PG in the normal range is important to prevent immediate and long-term consequences of hypoglycemia or hyperglycemia on neurodevelopment. The specific management strategy for abnormal glucose levels depends on the underlying etiology, and interventions could include nutritional changes, medications, hormone therapy, or even surgery.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the amino acid substrates for gluconeogenesis.
- Know the fuels used for brain metabolism.
- Know the relationship of maternal blood glucose to fetal glucose uptake and metabolism.
- Know the normal range of endogenous glucose production in term and preterm infants.
- Know the causes (including hyperinsulinemic hypoglycemia) of neonatal hypoglycemia syndromes.
- Recognize the clinical and laboratory features of neonatal hypoglycemia.
- Recognize the approach to therapy and prevention of neonatal hypoglycemia.
- Know the potential sequelae of neonatal hypoglycemia.
- Know the causes, including genetic disorders and other clinical conditions, of neonatal hyperglycemia, including transient diabetes mellitus.
- Know the clinical and laboratory features and approach to therapy of neonatal hyperglycemia, including transient diabetes mellitus.

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NeoReviews Quiz

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1. Hypoglycemia is a common problem in the newborn period. With the abrupt interruption of the constant transplacental supply of glucose, rapid metabolic adaptation must occur to maintain stable plasma glucose levels postnatally. Subsequently, the maintenance of normoglycemia requires a dynamic balance between nutrient intake and hormones. Which of the following statements regarding postnatal metabolic adaptation is correct?
    A. Gluconeogenesis is an important mechanism of glucose metabolism immediately after birth.
    B. Cortisol decreases the transcription of enzymes involved in glycogenolysis.
    C. The levels of glucagon and epinephrine increase after birth, and these hormones mobilize glucose through glycogenolysis.
    D. Growth hormone inhibits lipolysis.
    E. Beta oxidation of free fatty acid does not occur during the neonatal period.
2. Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in the newborn period. HI can be transient or permanent. Which of the following statements regarding HI is correct?
    A. HI is characterized by elevated insulin concentration, plasma ketones, and free fatty acids.
    B. Neonates with HI have a positive response to a glucagon challenge.
    C. Neonates with HI are typically small for gestational age.
    D. Transient HI secondary to stress is not typically responsive to diazoxide.
    E. The most common cause of inherited HI is growth hormone deficiency due to panhypopituitarism.
3. Laboratory evaluations are necessary to establish the etiology of persistent hypoglycemia in the neonate. First-tier laboratory evaluation, the so-called critical sample, includes the measurement of insulin, β-hydroxybutyrate, free fatty acid, cortisol, growth hormone and lactate levels at time of confirmed hypoglycemia (< 50 mg/dL). Which of the following statements regarding the laboratory evaluation of persistent hypoglycemia in the neonatal period is correct?
    A. Capillary blood sugar measured by glucose meter has been shown to be about 10% higher than plasma glucose levels.
    B. High insulin level during critical laboratory evaluation is most indicative of either panhypopituitarism or isolated growth hormone deficiency.
    C. A high free fatty acid level is pathognomonic for a fatty acid oxidation defect.
    D. High insulin levels along with absent ketones point toward HI.
    E. High lactate levels in the setting of hypoglycemia and low insulin levels are suggestive of adrenal insufficiency.
4. Transient hyperglycemia is a common problem in low-birthweight, preterm, and critically ill neonates. In contrast, neonatal diabetes mellitus (NDM) is rare and is, by definition, diagnosed before age 12 months. NDM should be suspected in neonates with hyperglycemia greater than 250 mg/dL (13.8 mmol/L) and persisting for more than 7 to 10 days after birth. Which of the following statements regarding NDM is correct?
    A. Infants with transient NDM present earlier than those with permanent NDM.
    B. Infants with transient NDM typically outgrow their need for insulin by 18 to 24 months of age.
    C. Most cases of transient NDM are due to maternal uniparental disomy in chromosomal region 6q24.
    D. Insulin gene mutations are a common cause of permanent NDM when there is a history of parental consanguinity.
    E. DEND (developmental delay, epilepsy, neonatal diabetes) syndrome is caused by a mutation in *ABCC8*.

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5. Hyperglycemia in neonates can be insidious and only detected on routine laboratory tests or urinalysis. Neonates with hyperglycemia are at risk for dehydration, acidosis, failure to thrive, and poor weight gain, as well as adverse neurodevelopmental outcomes. Which of the following mechanisms has not been implicated in hyperglycemia-mediated adverse consequences?

   A. Increased plasma osmolality.
   B. Endothelial injury.
   C. Dehydration
   D. Increased oxidative stress.
   E. Intracellular alkalosis.

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