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Glucose Metabolism

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INTRODUCTION

Cornblath and Reisner established nearly 60 years ago that neonatal hypoglycemia was a significant cause of neonatal morbidity and mortality, yet the definition and management of neonatal hypoglycemia have remained unclear. The management of low blood glucose levels is one of the most frequently encountered issues in the newborn nursery. The blood levels of glucose upon which we base our decision making remain a matter of expert opinion rather than being evidence based. The truth is the data needed to establish blood glucose levels that should be treated in the newborn have not been definitive enough to gain consensus.

In fact, the lack of consensus has led to further confusion for the clinician, as two pediatric organizations, the Committee of the Fetus and Newborn of the American Academy of Pediatrics (COFN AAP) and the Pediatric Endocrine Society (PES) have provided expert opinion on the management of neonatal hypoglycemia that suggested different ranges of actionable blood glucose levels (Figs. 4.1, 4.2).

We will examine the controversies and discuss screening and management of neonatal hypoglycemia. An understanding of transitional neonatal hypoglycemia and postnatal glucose homeostasis is essential to develop strategies to keep infants out of the NICU because of hypoglycemia while still preventing neurologic sequelae.

CASE 1

A 34-year-old primigravida after an uncomplicated pregnancy is admitted in labor at 36 weeks' gestation. The perinatal screening tests are negative, including a negative screen for group B *Streptococcus* (GBS) at 35 weeks' gestation. Membranes rupture occurred 2 hours before vaginal delivery. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The male infant weighs 2700 grams. The mother has planned to exclusively breastfeed the baby, and she begins in the delivery room with what is described as a "sluggish" first feed. Shortly thereafter, mother and baby are transferred to a postpartum room.

Before the baby being breastfed at 4 hours of age, the nurse on a routine assessment thinks the baby has slight tremors and she performs a point-of-care (POC) glucose level and it is 36 mg/dL. Apparently, the infant looks well enough to breastfeed because the nurse advises the mother to feed again. The nurse also suggests that after this breastfeeding the mother should supplement the infant with 1 oz of a term infant formula. She tells the mother that she will check the glucose again 1 hour after the formula feed to make sure the baby is no longer hypoglycemic. The mother is very disappointed that she will have to abandon her plan to exclusively breastfeed and wonders if it is absolutely necessary to give the formula. The follow-up POC glucose level is 52 mg/dL 1 hour after the formula feeding supplement, and the nurse's note does not document any further tremors.

The nurse calls you at home and discusses the findings and tells you that the mother is disappointed about having to give formula supplement to her baby. You have your smartphone with you and you pull up the Glucose APP, "Sugar Wheel" (Fig. 4.1) based on the algorithm from the Clinical Report—Postnatal Glucose Homeostasis in Late-Preterm and Term Infants published in *Pediatrics* in March 2011 from the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (COFN) (Fig. 4.2).

Exercise 1

Questions

1. Should this late preterm infant have been screened sooner than age 4 hours?
2. Is this infant symptomatic, and does the infant's glucose level (<40 mg/dL) require an immediate intervention?
3. Should a plasma glucose concentration have been sent to the laboratory at the same time as the POC glucose in this baby?
4. Should the infant simply have been left to continue breastfeeding, and are there other options?
5. Do infants who are exclusively breastfed have lower plasma glucose concentrations than those fed infant formulas?

Answers

1. Yes, this baby met high-risk criteria for neonatal hypoglycemia and should have been screened sooner because the baby was late preterm.
2. Yes, the tremors could be symptoms of hypoglycemia. Because symptoms of neonatal hypoglycemia are nonspecific, they often occur in newborns who are

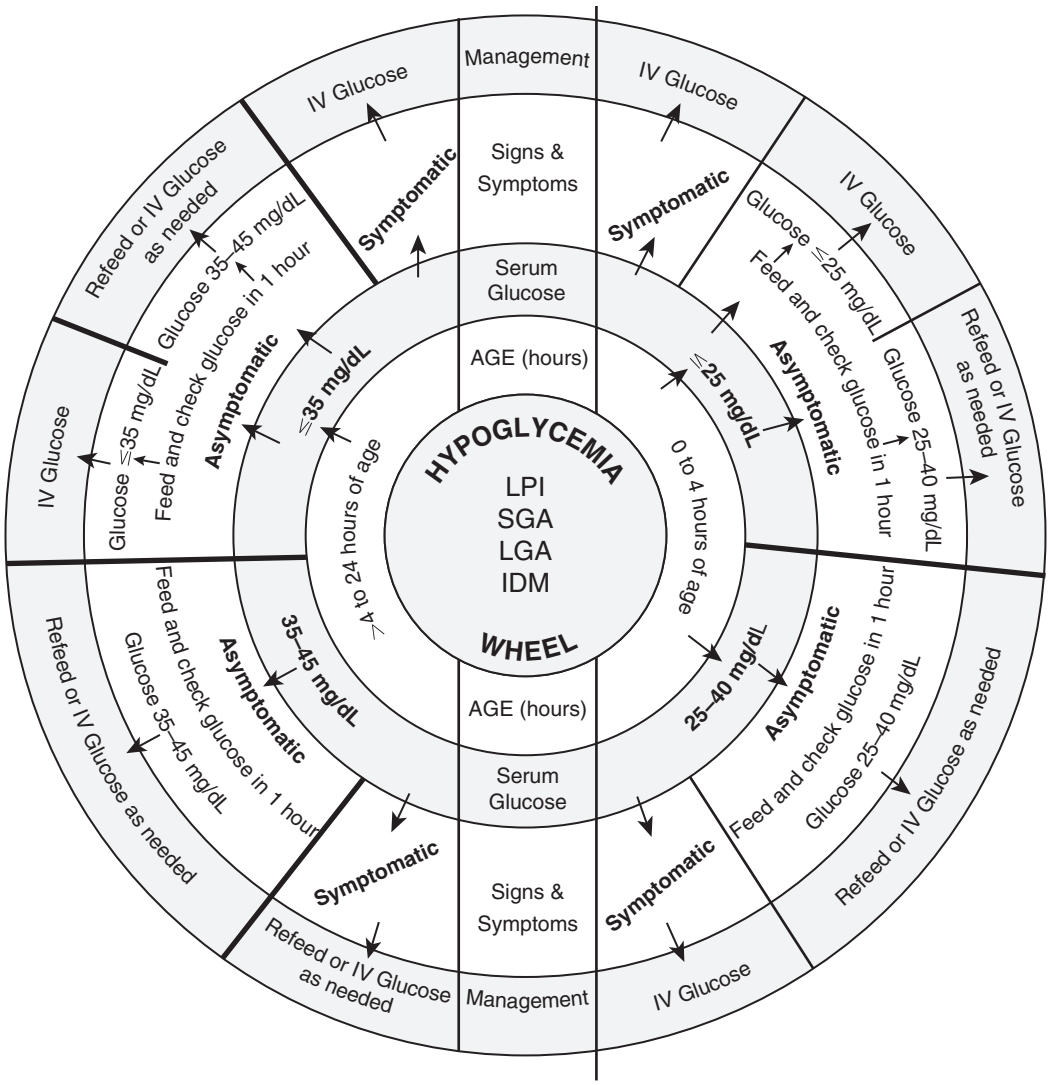

Fig. 4.1 Sugar Wheel nomogram for postanatal glucose homeostasis.

normoglycemic and have other problems. Jitteriness is just as likely among normoglycemic infants and those with a variety of other conditions. In addition, equally low blood glucose values are found in infants with no clinical signs ("asymptomatic hypoglycemia"). Therefore the presence or absence of symptoms cannot necessarily be used to discriminate between normal and abnormal blood glucose levels.

3. If symptoms are suspected and POC level is under 40 mg/dL, an immediate plasma glucose should be sent to the laboratory.
4. Yes, it is possible to have just continued the breastfeeding, because the symptoms were very mild and were actually associated with acceptable glucose levels. Other strategies might have included use of dextrose gel or donor human milk.
5. Breastfed infants may have lower plasma glucose levels than formula-fed infants.

After birth, the normal newborn infant's plasma glucose concentration falls below levels that were prevalent in fetal life. This is part of the normal transition to an extrauterine existence, and through a series of triggers, the infant activates endocrine and metabolic events associated with successful adaptation. When this adaptation fails, perhaps secondary to immaturity or illness, there is a limitation of substrate supply, which may disturb cerebral function and potentially result in neurologic sequelae. A low plasma glucose may be indicative of this process but is not per se diagnostic. What is meant by "low"? How low is "too low"? At what glucose level does hypoglycemia lead to irreversible changes in brain structure or function?

CASE 2

A term, appropriate for gestational age (AGA) male was born by elective cesarean section after an uneventful pregnancy to

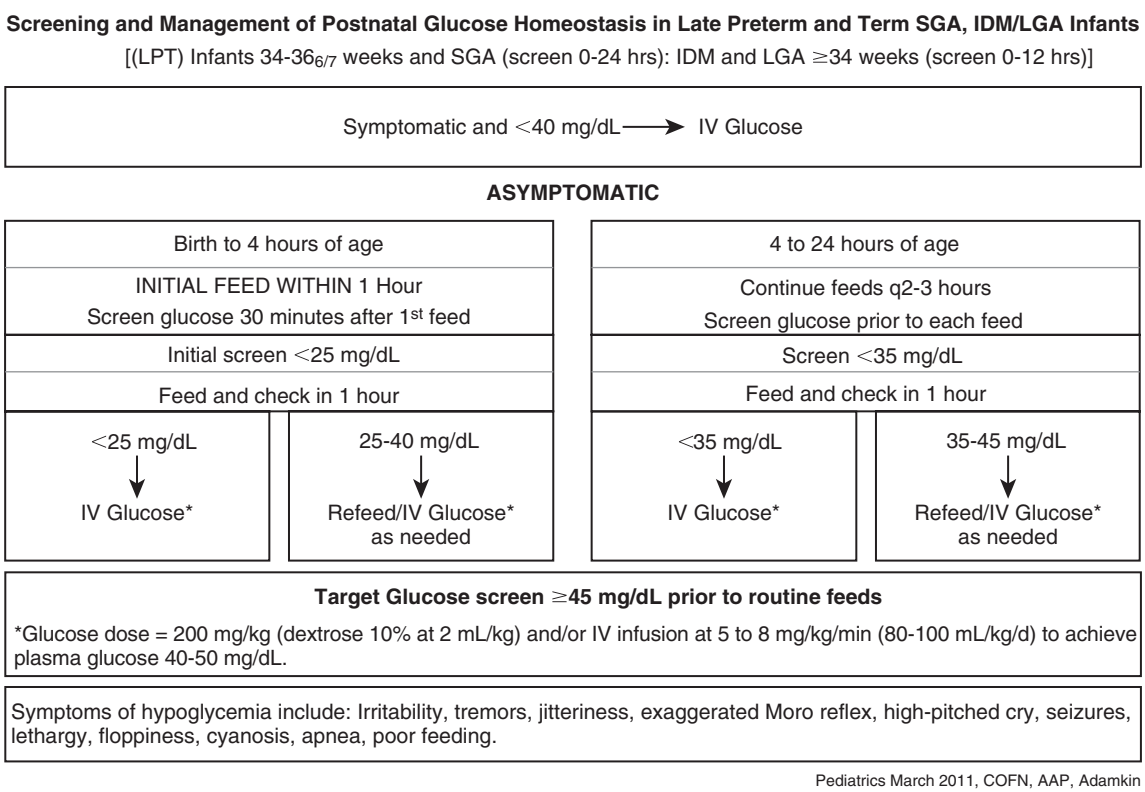

Fig. 4.2 Screening and management of postnatal glucose homeostasis from the AAP Committee on Fetus and Newborn. (From Adamkin DH: Postnatal glucose homeostasis in late-preterm and term infants, *Pediatrics* 127[2]: 576, 2011).

a 30-year-old gravida 3 para 2 woman. Prenatal screening studies were normal, and Apgar scores were 6, 7, and 8 at 1, 5, and 10 minutes respectively. The baby seemed to have "wet lungs" in the delivery room and briefly received blow-by oxygen. By 3 minutes of age, oxygen saturations values were normal, and the respiratory distress resolved. On admission to the well-baby nursery at 30 minutes of age, this well-appearing infant had a POC glucose done apparently because of the cyanosis in the delivery room, and it was 27 mg/dL. A plasma glucose was then sent off ,and it was 29 mg/dL. The infant was fed formula at 1.5 hours of age, and the repeat POC at 2 hours of age was 39 mg/dL.

Exercise 2

Questions

1. Was this baby's initial POC screen necessary?
2. When should screening for hypoglycemia take place, and was this infant's screen obtained at the physiologic nadir for plasma glucose values?

Answers

1. The initial screen was not necessary, as this baby was asymptomatic and had not yet been fed.
2. In high-risk populations, screening for hypoglycemia should take place after the first feed. Yes, this sample taken within the first hour of life would represent the physiologic nadir for plasma glucose values.

POSTNATAL GLUCOSE HOMEOSTASIS AND TRANSITIONAL NEONATAL HYPOGLYCEMIA

Maintenance of glucose homeostasis via initiation of glucose production is one of the critical transitional physiologic events that must take place as the fetus adapts to extrauterine life. It is not uncommon for the transition to be difficult and result in an alteration in glucose homeostasis and an infant with a low plasma glucose level.

The fetus depends on maternal supply and the placental transfer of glucose, amino acids, free fatty acids, ketones, and glycerol for its energy supply. The normal lower limit of fetal glucose concentration is approximately 54 mg/dL (3 mmol/L) over most of gestation. Fetal glucose production does not take place under normal conditions.

The ratio of insulin to glucagon in the fetal circulation plays a critical role in regulating the balance between glucose consumption versus energy stored. The high fetal ratio results in activation of glycogen synthesis and suppression of glycogenolysis through the regulation of hepatic enzymes used for these pathways (Fig. 4.3). Therefore in the fetus glycogen synthesis is enhanced and glycogenolysis is minimized. There is a rapid increase in hepatic glycogen during the last 30% of

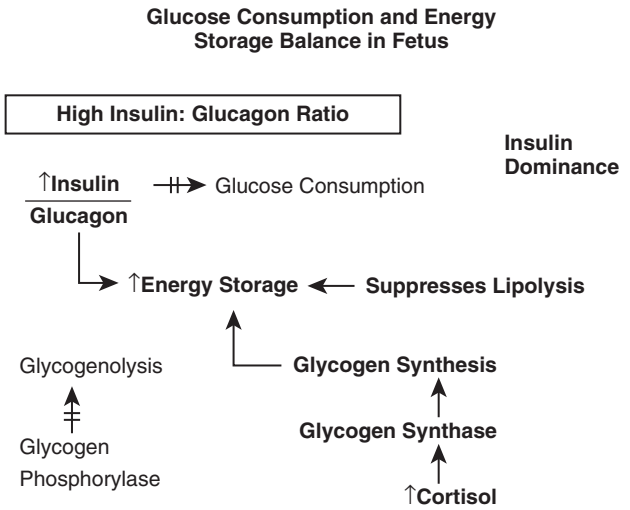

Fig. 4.3 Fetal maintenance of anabolic state promoting energy storage.

fetal life. This marked increase is associated with an increase in both circulating insulin and cortisol. The high insulin/glucagon ratio also suppresses lipolysis, which allows for energy to be stored as subcutaneous fat. This subcutaneous and hepatic reservoir establishes a ready substrate supply for the fetus to transition metabolically and establish postnatal glucose homeostasis (Fig. 4.3).

The dependence of the fetus on maternal glucose necessitates significant changes in regulation of glucose metabolism at birth following the abrupt cessation of umbilical glucose delivery. A number of physiologic changes allow the newborn to maintain glucose homeostasis (Fig. 4.4). Catecholamine concentrations increase immediately after delivery, and this stimulates glucagon secretion. Therefore the insulin/glucagon ratio falls postnatally. This ratio is important because it drives events both in utero and during the postnatal adaptation to a decreasing glucose supply.

When glycogen synthase is inactivated and glycogen phosphorylase is activated following birth, this leads to stimulation of glycogenolysis and inhibition of glycogen synthesis, which is the exact opposite of the in utero fetal milieu. The release of glucose from glycogen provides a rapidly available source of glucose for the neonate the first few hours after delivery. The estimates are that for the term infant the hepatic glycogen supplies enough glucose for the first 10 hours. It is very important that other mechanisms eventually come into play to maintain glucose homeostasis (Fig. 4.4).

The next important pathway for postnatal glucose homeostasis is gluconeogenesis. The high insulin/glucagon ratio after delivery induces enzymes required for gluconeogenesis. Free fatty acids are released secondary to surging catecholamines, which also increase glycerol and amino acid levels. By 4 to 6 hours of life, the term infant is capable of significant gluconeogenesis.

Until an exogenous supply of glucose is provided, either enterally or intravenously, hepatic glucose production is the most significant source of glucose to meet the needs of the infant. To maintain normal levels of hepatic glucose production, the infant must have the following:

- Adequate stores of glycogen and gluconeogenic precursors (fatty acids, glycerol, amino acids, and lactate)
- Concentrations of hepatic enzymes necessary for glycogenesis and gluconeogenesis
- Normally functioning endocrine system (counterregulatory hormones, human growth hormone [HGH], and cortisol)

If any of these systems are not in place, then there is a disruption of glucose homeostasis, which increases the chances for neonatal hypoglycemia.

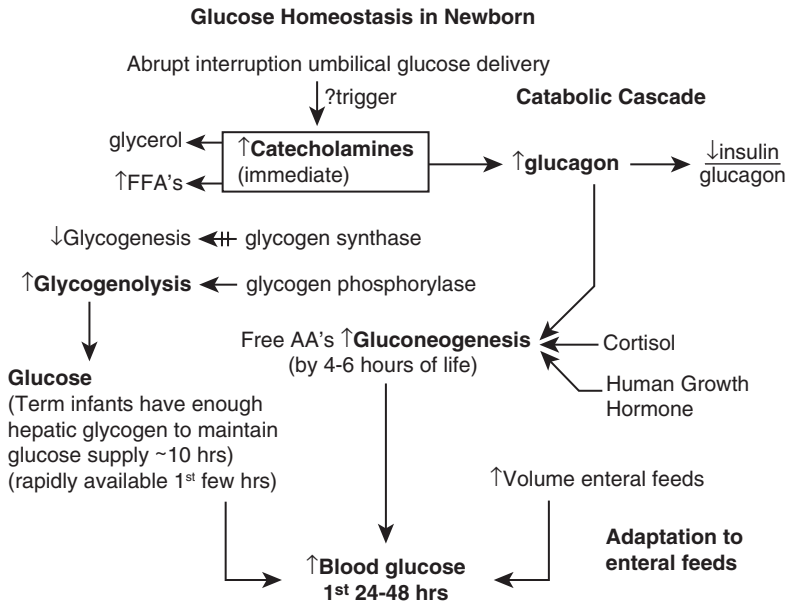

Fig. 4.4 Adaptations around delivery and over the first 24 hours of life to establish postnatal glucose homeostasis.

It has long been thought that preterm infants during the first 3 days of life had lower glucose values than term infants and they tolerated these lower levels better. This misconception came from the observation of lower plasma glucose levels in preterm infants who were commonly starved the first few days of life. These low values are no longer observed in preterm infants because of early intravenous nutrition and/or enteral feedings. However, within the first few hours after birth, the preterm infant has a significantly greater fall in glucose levels than in term infants, suggesting that they are less able to adapt to the cessation of intrauterine nutrition. Gluconeogenic ability is limited in preterm infants, possibly because of immaturity of the enzymatic pathways.

AAP RECOMMENDATIONS FOR SCREENING AND MANAGEMENT

The physiologic responses described earlier were used by the AAP to determine the ranges for action and considered the rising levels for the asymptomatic infant from birth to 4 hours of age (transition), and then 4 to 24 hours of age (Fig. 4.2). The AAP chose to name the figure Screening and Management of Postnatal Glucose Homeostasis rather than using the word hypoglycemia in the title. It seemed more logical to address the adaptation rather than to recommend absolute glucose levels needing treatment.

The AAP view of postnatal glucose homeostasis is that the infant's blood glucose concentration is about 70% of the maternal level at birth and falls rapidly to a nadir by 1 hour of age as low at 20 to 25 mg/dL (Fig. 4.5, 4.6). This nadir is prevalent in healthy neonates and seen in all mammalian newborns. These levels are transient and begin to rise over the first hours and days of life. This observation is considered part of the normal adaptation for postnatal life that helps establish postnatal glucose homeostasis. Are there advantages to having a lower blood glucose concentration compared with adults the first 48 hours? A decrease in glucose concentration soon after birth might stimulate physiologic processes that are required for survival, including promoting glucose production through gluconeogenesis and glycogenolysis. Furthermore, the decrease in glucose concentration enhances oxidative fat metabolism, stimulates appetite, and may help adapt to fast-feed cycles.

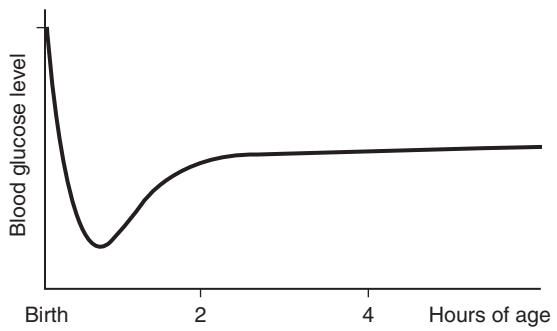

Fig. 4.5 Blood glucose concentration transition from fetus to neonate over the first hours of life. (From Srinivasan G, Pildes RS, Cattaman G: Plasma glucose values in normal neonates: a new look, *J Pediatr* 109[1]:114–117, 1986.)

The AAP guideline during the first hours of transition uses the lower ranges of glucose values, not the mean values from fetal and neonatal data (Fig. 4.6). It also emphasizes the clinical examination and condition of the infant. The AAP also investigated whether there was any reliable level of neuroglycopenia (the critical threshold of plasma glucose where brain injury occurs). No absolute level has been identified.

PEDIATRIC ENDOCRINE SOCIETY RECOMMENDATIONS FOR SCREENING AND MANAGEMENT

Following publication of the AAP recommendations, the PES provided a detailed description of this transitional neonatal hypoglycemia by examining metabolic and hormonal responses at various levels of plasma glucose (Table 4.1). The strategy is routinely used in pediatric endocrinology for evaluation of hypoglycemia in older infants and children. This helps explain differences between the two organizations in their recommendations. The PES focuses on the concentration of glucose at which metabolic counterregulation occurs and that is used to define a "safe" lower limit for blood glucose concentration.

This unique period occurs during the first 48 hours in all mammals, not just human babies. It is characterized by a relative hyperinsulinism (transitional hyperinsulinism), low levels of ketones, inappropriate preservation of glycogen, and mean blood glucose levels at the nadir of 55 to 65 mg/dL. This resembles a known form of congenital hyperinsulinism in which the plasma glucose threshold for suppression of insulin secretion is lowered. This 55 to 65 mg/dL range, which is the mean range at the nadir, turns out to be the same level below which adults and older children demonstrate neurogenic symptoms. Therefore this observation along with the rest of the metabolic profile led the PES to suggest this was the critical range of glucose to maintain in newborn infants the first 48 hours.

The PES further argued that this range is where adults and older children activate neuroendocrine and metabolic mechanisms profiles for brain protection. The endocrine society also recognized that by 72 hours or so of life, glucose levels in the newborn rise to levels similar in older children and adults. Therefore the PES concluded that hyperinsulinemia accompanied by suppressed levels of ketones and inappropriately large glycemic responses to glucagon and epinephrine were consistent with a hypoketotic hyperinsulinemia.

When this transient form of hyperinsulinism ends and the glucose stimulus for insulin secretion matures, plasma glucose levels rise to over 70 mg/dL. Distinguishing transient neonatal hypoglycemia from a suspected persistent hypoglycemic disorder during an infant's first 48 hours is very difficult. The PES thus recommends delaying any diagnostic evaluation until after 2 to 3 days of life to diagnose a *persistent hypoglycemic disorder.*

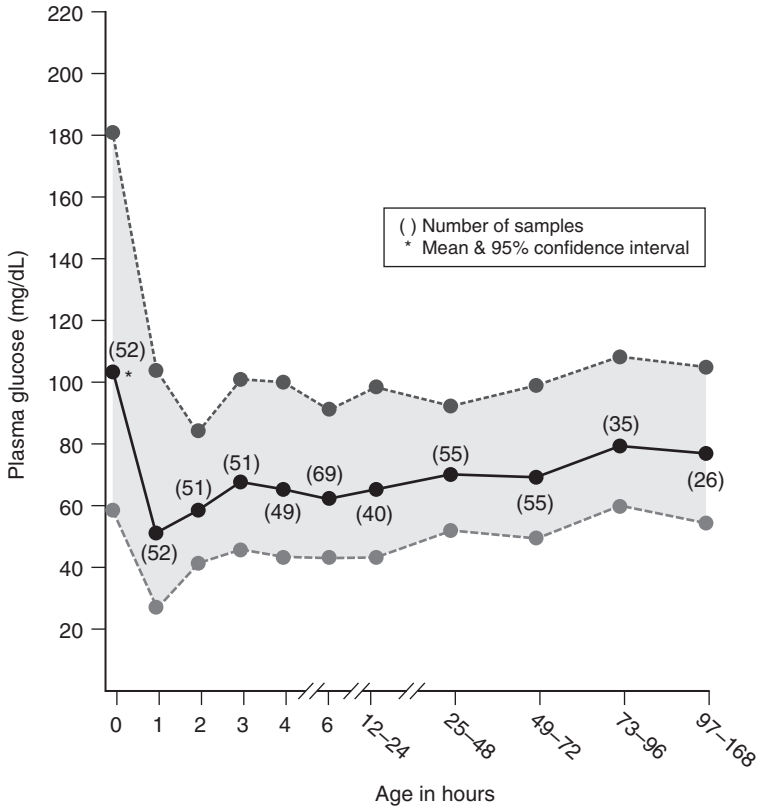

Fig. 4.6 Plasma glucose concentrations in full-term, appropriately grown newborns without any prenatal or neonatal complications. (Adapted from Srinivasan G, Pildes RS, Cattaman G: Plasma glucose values in normal neonates: a new look, *J Pediatr* 109[1]: 115, 1986; and Marconi AM, Bozetti P, Ferraro MM, et al: Relationship of maternal fetal glucose concentrations in the human from midgestation until term, *Metabolism* 37[4]: 358–363, 1988.)

TABLE 4.1 Postnatal Glucose Treatment Targets: PES

High-risk newborns without a suspected congenital hypoglycemia disorder	0–48 h	>50 mg/dL
	>48 h	>60 mg/dL
Neonates with suspected congenital hypoglycemia disorder and those requiring IV glucose to treat hypoglycemia	Any time	>70 mg/dL
The PES Set the above Thresholds Based on the Following Observations about the Impact of Specific Glucose Concentrations in Adults:		
55–65 mg/dL	Brain glucose utilization becomes limited	
50–55 mg/dL	Neurogenic symptoms (palpitations, tremor, anxiety, sweat, hunger, paresthesia) perceived	
<50 mg/dL	Cognitive function impaired (neuroglycopenia, characterized by confusion, seizures, coma)	

IV, Intravenous; *PES,* Pediatric Endocrine Society
Adapted from Stanley C, Rozance P, Thornton MB, et al: Reevaluating transitional neonatal hypoglycemia: mechanism and implications for management, *J Ped* 166:1–6, 2015.

The PES document also noted that the plasma glucose concentrations of normal newborns studied from the 1950s and 1960s (when babies were fasted between 8 and 27 hours) were remarkably stable (mean value was 57 mg/dL) and unaffected by the timing of initial feeding or the interval between feeds. However, this fails to recognize that feedings do affect infants whose glucose concentrations are low, and although this appears to be a regulated process, it is not for those at greatest risk from hypoglycemia.

The fundamental question of how best to manage asymptomatic newborns with low glucose concentrations remains unanswered. Balancing risks of overtreating newborns with

low glucose concentrations who are undergoing normal transition following birth against the risks of undertreating those in whom low glucose concentrations are pathologic, dangerous, and/or a harbinger of serious metabolic disease remains a challenge.

CASE 3

You are called to an emergency delivery for a 21-year-old primigravida woman at term gestation with no prenatal care and evidence of fetal distress. Rupture of membranes occurred 10 hours before delivery and Apgar scores were 6 and 7 at 1 and 5 minutes of life respectively. The male infant is vigorous in the delivery room with scant meconium staining, but the infant is macrosomic. The mother did not know if she had any abnormalities with glucose levels before or during the pregnancy. The baby weighs 4240 grams, and the length and head circumference (HC) are at the 50th percentile on the postnatal growth curves. The infant feeds sluggishly at 1 hour of age. At 6 hours of age, before the next feeding, he appears lethargic and jittery. He is offered a term formula but feeds poorly; the POC glucose level is 10 mg/dL.

Exercise 3

Questions

1. What risk factors does this baby have for postnatal hypoglycemia?
2. When should this baby have been fed?
3. When should first screen for hypoglycemia have been performed?
4. Why is this symptomatic?
5. How should this infant be managed at 6 hours of life?
6. If treated and corrected by hour 48 of life, will the glucose level at 6 hours of life cause brain injury?

Answers

1. This infant is macrosomic with a disproportionately smaller HC and length, so you are concerned about gestational diabetes. Maternal diabetes is a risk factor for both the AAP COFN and PES.
2. This infant was described as vigorous in the delivery room and therefore despite being macrosomic was able to feed within the first hour of life. There was no reason to immediately screen for a low glucose value, because the baby was asymptomatic.
3. The infant should have been screened 30 min after the first feeding, which was described as sluggish.
4. It is very likely this infant is hyperinsulinemic. Moreover, he has only received one small feeding before becoming symptomatic at 6 hours of age when the next feeding was offered.
5. This symptomatic hypoglycemic infant needs immediate attention with intravenous glucose.
6. No, we don't know the likelihood of brain injury except that prolonged and symptomatic hypoglycemia with seizures increases the risk of neurologic impairment (Box 4.1).

BOX 4.1 Conditions That Should Be Present Before Considering That Long-Term Neurologic Impairment Might Be Related to Neonatal Hypoglycemia

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

From Rozance P, Hay W: Hypoglycemia in newborn infants: features associated with adverse outcomes, *Biol Neonate* 90:84, 2006.

DEFINITION OF HYPOGLYCEMIA

A consistent definition of hypoglycemia does not exist in the literature or in clinical practice. When the first neonates were recognized as having significant hypoglycemia in the mid-1950s, the infants had striking clinical manifestations, often seizures, and their blood sugar values were consistently below 20 to 25 mg/dL (1.1–1.4 mmol/L). The abnormal signs cleared quickly after increasing the blood glucose concentration to above 40 mg/dL (2.2 mmol/L). Now 60 years later, after 40 mg/dL became the "critical" level for hypoglycemia, our understanding of the metabolic disturbances and genetic defects underlying aberrations in postnatal glucose homeostasis has increased dramatically. However, this increase in knowledge, if anything, has led us further from what we need to know about blood glucose concentrations in the newborn infant. How low is too low?

In a review of current textbooks, there is no consensus definition for hypoglycemia; recommended values range from 18 mg/dL (1 mmol/L) to 70 to 100 mg/dL (3.8–5.5 mmol/L). It is interesting to note that the definition of neonatal hypoglycemia has gone up decade by decade over the last 40 years (Fig. 4.7). The easiest diagnosis of hypoglycemia may be the situation in which the symptoms associated with a low blood

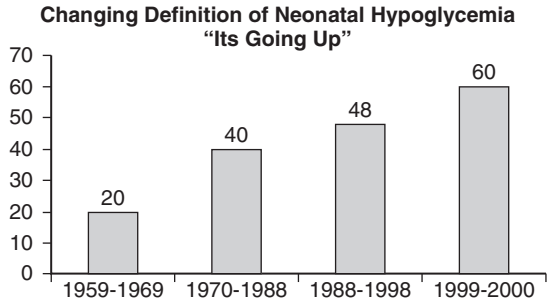

Fig. 4.7 Plasma glucose concentrations considered representing hypoglycemia over the last 40 years.

sugar resolve when the blood sugar concentration is increased. Apart from this clinical situation, the diagnosis of hypoglycemia is much more complex.

OPERATIONAL THRESHOLDS

Hypoglycemia represents an imbalance between glucose supply and utilization and may result from many different regulatory mechanisms (Box 4.2). In 2000 Cornblath proposed an operational definition for neonatal hypoglycemia. An operational threshold is an indication for action but is not diagnostic of a disease. One uses available clinical and experimental data to define the lower level of normoglycemia. The belief is that the neonate can safely tolerate these levels at specific ages and under established conditions.

Cornblath first suggested an operational level for plasma glucose of 30 to 36 mg/dL during the first 24 hours of life for healthy full-term or late preterm (34–37 weeks' gestation) formula-fed infants. If the glucose concentration fell below that operational level after a feeding or recurred, he suggested increasing the plasma glucose levels above 45 mg/dL. This absolutely does not imply that the lower plasma glucose concentrations alone produce mental or developmental abnormalities. He also suggested that the operational threshold might be increased to 45 to 50 mg/dL (2.5–2.8 mmol/L) or higher in a sick, low birth weight, or premature infants suspected of having increased glucose requirements as a result of sepsis, hypoxia, or other major systemic illness.

Finally, he recommended that beyond 24 hours of age, this operational threshold may be increased to 40 to 50 mg/dL. Values below the operational threshold level are an indication to raise the plasma glucose levels and do not imply neuroglycopenia or that neurologic injury is likely. Infants at all ages and gestations with repetitive, reliable plasma glucose values less than 20 to 25 mg/dL should be given parenteral glucose and monitored at regular intervals to ensure that these low values do not persist or recur.

When the low plasma glucose levels are prolonged or recurrent, they may result in acute systemic effects and neurologic sequelae. Cornblath stresses that it is not possible to define a plasma glucose level that requires intervention in every newborn infant because there is uncertainty over the level and duration of hypoglycemia that causes damage, and little is known of the vulnerability of the brain at various gestational ages. He emphasized that significant hypoglycemia is not and can never be defined by a single number that can be applied universally to every individual patient. Rather, it is characterized by a value(s) that is unique to each individual and varies with both their state of physiologic maturity and the influence of pathology. It can be defined as

BOX 4.2 Pathogenesis of Hypoglycemia in Neonates

Excess Utilization	Inadequate Production or Substrate Delivery
Hyperinsulinism: IDM, erythroblastosis, LGA, SGA, or islet cell or other endocrine pathology	Inadequate or delayed feedings or parenteral delivery of calories
Increased calorie expenditure for thermoregulation in LBW and SGA infant	Aberrant hormonal regulation of glucose or lipid metabolism: hypothalamic, pituitary, and peripheral endocrine disorders
Increased calorie expenditure because of excess muscle activity: increased work of breathing in respiratory distress, drug withdrawal, CNS irritability	Transient developmental immaturity of critical metabolic pathways reducing endogenous production of glucose and/or other substrates
Circulatory or respiratory diseases that shift energy metabolism from aerobic to anaerobic pathways: hypoxemia, hypotension, hypoventilation, septic shock	Deficient metabolic reserves of precursors or glucose-sparing substrates
Relative excess of glucose-dependent tissues: high brain:liver ratio in SGA infants	Deficient brain glucose transporters: posthypoxia-ischemia, inherited glucose transporter defects
Inborn errors of metabolism resulting in inadequate glucose-sparing substrates: free fatty acids, ketones, glycerol, amino acids, lactate	Suppression of gluconeogenesis, glycogenolysis, and hepatic glucose release by inappropriately high circulating insulin levels in conditions associated with hyperinsulinism
Acute brain injury causing increased brain glucose utilization: seizures, intoxication, meningitis, encephalitis, or hypermetabolism following acute brain injury (hypoxia-ischemia, trauma, hemorrhage)	

CNS, Central nervous system; *IDM,* infant of diabetic mother; *LBW,* low birth weight; *LGA,* large for gestational age; *SGA,* small for gestational age

From Cornblath M, Ichord R. Hypoglycemia in the neonate, *Semin Perinatol* 24(2):138, 2000.

the concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the abnormal milieu caused by the inadequate delivery of glucose to a target organ (for example, the brain).

Treatment should be guided by clinical assessment and not by glucose concentration alone. The infant displaying neurologic signs requires more urgent elevation of plasma glucose concentration than the asymptomatic one, regardless of the individual plasma glucose concentration.

The National Institutes of Health conference on Knowledge Gaps and Research Needs for Neonatal Hypoglycemia concluded the following concerning operational thresholds: "The so-called operational thresholds are useful guidelines to take appropriate actions. However, the recommendations are not based on evidence of significant morbidity if no actions are taken. Similarly, there is no evidence that outcomes improve if actions are taken at the operational threshold value. All published definitions providing singular values or ranges have been arbitrary and developed for analytical and grouping purposes."

RESOLVING DIFFERENCES IN THE AAP AND PES RECOMMENDATIONS FOR CRITICAL GLUCOSE THRESHOLDS

Recently the AAP COFN ratified for another 5 years their statement on postnatal glucose homeostasis (Fig. 4.2). Around the same time, a reevaluation of transitional hypoglycemia was published by the PES (Table 4.1). A recent editorial called "Imperfect Advice" contrasts the two organizations' approaches.

The AAP clinical report is not inclusive of all preterm infants, but it focused on late preterm as well as small for gestational age (SGA) and large for gestational age (LGA) term infants and infants of diabetic mothers (IDM) at-risk patients. Of course, symptomatic infants are all screened. Preterm infants under 34 weeks' gestation were not included in the algorithm, based on the assumption that the vast majority of more immature infants would be cared for in the NICU, where routine screening is in place. The PES expanded the list for screening to not only include symptomatic infants and the same risk groups as the AAP document but suggested screening those infants experiencing perinatal stress (birth asphyxia, cesarean section for fetal distress), maternal preeclampsia, meconium aspiration syndrome, prematurity or postmaturity, family history of genetic hypoglycemia, congenital syndromes, or abnormal physical features (Box 4.3). The PES does not offer screening times. Its targets for therapy include under 50 mg/dL the first 48 hours, and when intravenous fluids are required a value of over 60 mg/dL should be achieved. It emphasizes the need for careful attention so that cases of persistent hypoglycemia after 48 to 72 hours are not missed (Box 4.4 and 4.5). A major focus of the PES report was to prioritize strategies to diagnose persistent hypoglycemic syndromes before discharge in at-risk infants.

BOX 4.3 Neonates Who Are at Increased Risk of Hypoglycemia (PES)

1. Neonates with symptomatic hypoglycemia
2. Neonates who had perinatal stress
   - Birth asphyxia/ischemia; cesarean section for fetal distress
   - Maternal preeclampsia/eclampsia or hypertension
   - Intrauterine growth restriction (small for gestational age birth weight)
   - Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia
3. Congenital syndromes (such as Beckwith-Wiedemann), abnormal physical features (such as midline facial malformation, microphallus)
4. Family history of a genetic form of hypoglycemia
5. Large for gestational age birth weight
6. Premature or postmature delivery
7. Infant of diabetic mother

From Thornton PS, Stanley CA, De Leon DD, et al: Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *JPeds* 167:(6):238–245,2015.

The AAP guidance only applies to the first 24 hours of life. Actionable ranges of 25 to 40 mg/dL for the first 4 hours of life and then 35 to 45 mg/dL from 4 hours to 24 hours of age are the operational thresholds for the AAP. Glucose levels rise after the first 48 hours of life and should be similar to those of older children by 72 to 96 hours of age.

The AAP recommendation for treatment below the actionable range after feeding is based on individual risk assessment and examination of the infant. Target glucose concentrations when intravenous fluids are required should exceed 45 mg/dL.

What is clear with all recommendations is that the greater the glucose threshold that is set for screening and the more often these tests are done, the more often asymptomatic patients with low glucose levels will be identified. That has the potential to result in a neonatal intensive care admission and separation from mother for an asymptomatic infant and to be a hindrance to successful breast feeding.

PHYSIOLOGIC RESPONSES TO HYPOGLYCEMIA AND BRAIN INJURY

There is no easy way to study glucose insufficiency in human infants as a cause of acute neuronal injury. The glucose concentration is only an indicator of glucose insufficiency; the other factors to consider when determining glucose insufficiency include cerebral blood flow, cerebral glucose utilization rate, and cerebral uptake and metabolism of alternative fuels (see later), as well as the duration of the hypoglycemia and the presence of associated clinical complications. Plasma or blood glucose concentration, however, may be the only practical laboratory measure available to assess glucose insufficiency and response to treatment. A thorough physical examination assessing for signs and symptoms (Box 4.6) of

BOX 4.4 Classification of Persistent Neonatal Hypoglycemia

Hyperinsulinemia
Persistent hyperinsulinemic hypoglycemia of infancy
- Sporadic
- Familial
- Focal beta-cell adenoma
- Hyperammonemic hyperinsulinism

Beckwith-Wiedemann syndrome

Endocrine Disorders
Panhypopituitarism
Growth hormone deficiency
Adrenocorticotropic hormone deficiency
Adrenal insufficiency
Glucagon deficiency
Epinephrine deficiency

Glycogen Storage Disease (GSD)
Glucose-6-phosphatse deficiency (GSD type 1)
Debrancher deficiency (GSD type III)

Disorders of Gluconeogenesis
Fructose 1,6-diphosphatase deficiency
Pyruvate-carboxylase deficiency
Phosphoenol pyruvate-carboxykinase deficiency

Disorders of Fatty Acid Oxidation
Carnitine-acylcarnitine translocase deficiency
Very long-chain acyl-CoA dehydrogenase deficiency
Long-chain acyl-CoA dehydrogenase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Multiple acyl-CoA dehydrogenase deficiency

Disorders of Amino Acid and Organic Acid *Metabolism*
Maple syrup urine disease
Propionic academia
Methylmalonicacidemia
Isovalericacidemia
Multiple carboxylase deficiency
3-Hydroxy-3-methylglutaryl CoA lyase deficiency

Mitochondrial Disorders
3-Methylglutaconicaciduria

Glycosylation Disorders
Systemic Disorders
Hepatic failure
Congestive heart failure

CoA, Coenzyme A.
Uhing MR and Kleigman: Glucose, calcium, and magnesium. In Fanaroff AA and Fanaroff JM: *Klaus & Fanaroff's care of the high-risk neonate,* ed 6, 2012, Elsevier, p 295.

BOX 4.5 Neonates in Whom to Exclude Persistent Hypoglycemia Before Discharge

- Neonates with severe hypoglycemia (e.g., an episode of symptomatic hypoglycemia or requiring IV dextrose to treat hypoglycemia
- Neonates unable to consistently maintain preprandial plasma glucose concentrations >50 mg/dL by day 3
- Family history of a genetic form of hypoglycemia
- Congenital syndromes (e.g., midline facial malformations, microphallus)

BOX 4.6 Signs and Symptoms of Hypoglycemia in Newborn Infants

General Findings
Abnormal cry
Poor feeding
Hypothermia
Diaphoresis

Neurologic Signs
Tremors and jitteriness
Hypotonia
Irritability
Lethargy
Seizures

Cardiorespiratory Disturbances
Cyanosis
Pallor
Tachypnea
Apnea
Cardiac arrest

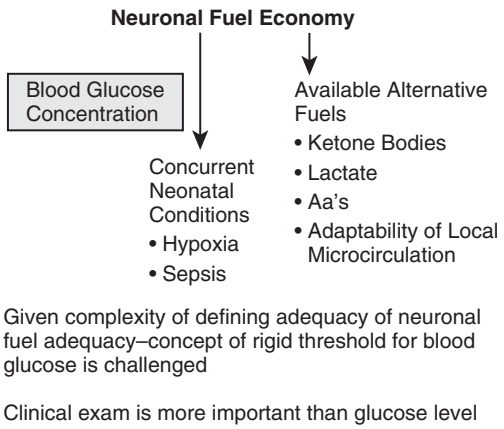

Fig. 4.8 Factors that play a role in energy available for the central nervous system including blood glucose concentrations.

hypoglycemia and particularly neurologic abnormalities may help distinguish those infants with low blood glucose concentrations who are adequately compensating. Fig. 4.8 shows the many factors (neuronal fuel economy) that must be considered in evaluating the infant with a low blood glucose concentration. The clinical examination of the infants is an important part of the approach advocated by the AAP.

Another important neuroprotective response to hypoglycemia is the capacity to accommodate changes in the rate of cerebral glucose metabolism by substituting alternate energy

substrates. The best characterized alternative fuel for the brain during hypoglycemia is lactate. Observations from animal data indicate that lactate entry into the tricarboxylic acid cycle may help compensate for decreased glucose metabolism. Lactate is the product of an astrocyte-neuronal lactate shuttle, which can supply the neurons with lactate for energy during periods of glucose deprivation. Brain glycogen is stored in the astrocyte, which makes this shuttle another important source of neuroprotection.

It appears that the human brain has the capacity to metabolize ketone bodies. Therefore the ability of the neonatal brain to utilize ketone bodies is almost certainly another form of neuroprotection during hypoglycemia. In healthy, term infants, plasma ketone bodies increase to a maximum concentration on days 2 and 3. Additionally, the ketone bodies increase further when the glucose concentration in the blood is low. However, preterm infants do not show similar patterns of ketone response and appear to have a lower capacity to mobilize ketones as an alternative fuel. It is also clear that formula feeding as a clinical intervention for hypoglycemia has a suppressive effect on early ketogenesis.

There are considerable differences in regional susceptibility in the brain to hypoglycemia that contribute to the pattern and distribution of injury, but the reported changes have not been consistent. Some animal and human neonatal imaging studies have indicated vulnerability to hypoglycemia in the occipital region, striatum, cingulate cortex, and hippocampus. However, recent clinical and imaging studies have indicated more diverse cerebral injury in infants with significant clinical symptoms of hypoglycemia. A study including 35 term infants with symptomatic hypoglycemia (86% of infants with a blood glucose <35 mg/dL and seizures) extended the spectrum of magnetic resonance imaging (MRI) abnormalities to the white matter, deep nuclear gray matter, and cortical infarction. Therefore an MRI should be a routine investigation for the newborn infant with symptomatic hypoglycemia to define the nature of any cerebral injury.

It must be emphasized, however, that studies like these relate to infants who sustained severe and prolonged hypoglycemia with encephalopathy. There is currently no imaging evidence that mild hypoglycemia of any duration causes brain injury or that asymptomatic hypoglycemia of any duration causes brain injury.

Identifying Risk Factors for Neonatal Hypoglycemia

The AAP COFN report on the management of hypoglycemia included late preterm (34–36$^{6}/_{7}$ weeks' gestation), infants of diabetic mothers (IDM), and small or large for gestational age term infants (SGA and LGA). It did not recommend against screening other at-risk groups but instead focused on the most likely newborns with asymptomatic hypoglycemia. A paper was published not long after the AAP guideline that prospectively looked at the incidence of hypoglycemia by their definition (plasma glucose concentrations less than 47 mg/dL). About 75% of the patients had measurement through 48 hours of life. Fifty-one percent of the patients had a glucose under 47 mg/dL, and 19% had a glucose level under 36 mg/dL, confirming the decision of the AAP to focus on these patients. This incidence of hypoglycemia was higher than other studies because of the higher numerical level defining hypoglycemia. Thirty seven percent of patients with hypoglycemia in this study had their first episode after three normal screens, and 6% had their first episode after 24 hours. This indicates that hypoglycemia may be a concern for longer periods than older studies suggest and that three normal screens may not be adequate. This study also found that there was no difference in the timing, severity, or incidence of low glucose among the four groups. The problem is the study was not designed to provide evidence that any numerical cutoff for hypoglycemia is more valid than another.

CASE 4

A 37-year-old gravida 4 para 4 woman delivers a 3400 g male infant with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively, after an uncomplicated pregnancy and labor. The mother has breastfed all of her other children successfully and breastfeeds this infant at 45 minutes of age in the delivery room. A bedside glucose is obtained right after the feeding and it is 27 mg/dL.

Exercise 4

Questions

1. Should this infant have been screened for hypoglycemia?
2. Should the screen occur immediately following the feeding?
3. How does glucose homeostasis differ in breastfed and formula-fed infants?
4. If you use the PES recommended levels will it change the actionable levels to treat low glucose levels, and does it address feedings?

Answers

1. This infant does not meet any of the risk categories for screening and management of postnatal glucose homeostasis and, importantly, is not symptomatic.
2. Glucose screens during the first 4 hours of life are taken 30 minutes after feedings. Thereafter, screens precede feedings for optimal management.
3. Breastfed infants are believed to have higher ketone levels than formula-fed infants, the principal alternate metabolic fuel for the brain, thus sparing the need for glucose. The AAP recommends breast milk within the first hour of life and a feeding interval between 2 and 3 hours to promote breastfeeding and maintain glucose levels. The PES noted that the breastfed infant consumes very few calories from colostrum during the first days after birth. However, despite being "relatively fasted, mean glucose values are remarkably stable." Therefore the PES concluded that glucose values are unaffected by feeding.
4. Using mean (PES) glucose values versus lower range (AAP) glucose values guarantees there will be significant differences in interpretation for actionable levels for

asymptomatic infants. Feeding is more important for patients in the lower ranges of plasma glucose and is affected by timing of initial feed and intervals of feeding.

NEURODEVELOPMENTAL OUTCOMES IN INFANTS WITH HYPOGLYCEMIA

As noted earlier, the AAP guideline during the first hours of transition uses the lower ranges of glucose values, not the mean from fetal and neonatal data. It also emphasizes the clinical examination and condition of the infant. The AAP also looked at neurodevelopmental data to determine whether there was any validated level of neuroglycopenia (the critical threshold of plasma glucose where brain injury occurs).

The fundamental question of how best to manage asymptomatic newborns with low glucose concentrations remains unanswered. Balancing risks of overtreating newborns with low glucose concentrations during the normal transition versus the risks of undertreating those in whom low glucose concentrations are pathologic and/or a harbinger of serious metabolic disease remains a challenge.

The neurodevelopmental outcome approach is to find the critical threshold of plasma glucose associated with brain injury or where neuroglycopenia occurs in the newborn. In the adult, this is 50 mg/dL. Neuroglycopenia is the level at which there is an inadequate supply of glucose for the brain. This level is not known for the newborn. The neurodevelopmental approach was profoundly influenced by a multicenter nutrition study from the UK published in 1988. The study evaluated blood glucose levels drawn daily initially then weekly until discharge on 661 infants under 1850 g at birth who were enrolled in a nutrition study looking at early diets and cognitive outcomes. They found that a critical glucose level under 47 mg/dL would reliably predict adverse outcomes. The number of days below this value was strongly related to reduced scores for mental and motor development at 18 months corrected age. Similar but less dramatic differences were found when the children were seen again as part of a larger study when the children were 7 to 8 years old. These findings have profoundly influenced neonatal care across the developed world ever since. This value of 47 mg/dL became a worldwide standard and was applied to term healthy (AGA) neonates as the gold standard critical threshold, even though this study had no term infants in it. The authors themselves suggested in a letter written later that there is "difficulty providing causation when an observational approach is used and that when such observations generate hypotheses or legitimate clinical concerns, this should stimulate future studies and randomized controlled trials."

Almost 25 years later from the UK came a prospective trial including infants under 32 weeks' gestation who had blood glucose levels measured daily for the first 10 days of life. Forty-seven had a blood glucose level under 47 mg/dL on at least 3 days of the first 10 days of life. All were matched for appropriate variables with those who never had a value under 47 mg/dL. No differences were found in developmental progress or physical disability at 2 years of age. Eighty-one percent of the cohort were matched again at 15 years of age, and they were almost identical for full-scale IQ. The inclusion of children who had a level under 47 mg/dL for more than 4 days and another group under 36 mg/dL on three occasions did not alter these results. They "found no evidence that recurrent low blood glucose levels, (<47 mg/dL) in the first 10 days of life pose a hazard to preterm infants." This study does not imply that low blood glucose levels cannot be damaging in preterm infants.

Studies from the Children with Hypoglycemia and Their Later Development (CHYLD) research group included serial follow-up and subcutaneous continuous monitoring with glucose sensors. These studies included a large prospective cohort of term and late preterm neonates at risk for hypoglycemia, the same groups identified by the AAP. They defined hypoglycemia as under 47 mg/dL plasma glucose concentration. Fifty-three percent of 404 at-risk infants (late preterm SGA and LGA infants and IDM) became hypoglycemic. They found no increase in risk for neurosensory impairment at 2 years of age with hypoglycemia. They also performed blinded interstitial continuous glucose monitoring and noted that intermittent blood sampling missed 25% of episodes of blood glucose levels under 47 mg/dL. Even with aggressive treatment, including dextrose gel, nearly 25% of infants experienced 5 hours of glucose concentration under 47 mg/dL. Risks of impairment were not increased even in those infants with hypoglycemia that was unrecognized (interstitial monitoring) and therefore not treated. It is noteworthy that higher glucose levels after treatment for hypoglycemia were associated with neurodevelopmental impairment. Those infants who spent a larger proportion outside the central range of 54 to 72 mg/dL in the first 48 hours of life had worse outcomes.

In a subsequent study, McKinlay et al evaluated 614 term and late preterm at risk for hypoglycemia using intermittent sampling and interstitial monitoring. The study included patients without hypoglycemia and both treated and untreated infants with hypoglycemia. Hypoglycemia was defined as plasma glucose under 47 mg/dL. Infants were screened and treated with the aim of keeping plasma glucose concentrations over 47 mg/dL. Surprisingly, there were long and undetected periods of hypoglycemia detected only on interstitial monitoring. Almost one out of four had hypoglycemic episodes not detected on intermittent sampling. Twenty-five percent of those undetected episodes lasted over 5 hours during the first week of life.

Neurosensory impairment or processing difficulty at age 2 was reported among four subgroups, including a reference group who never had hypoglycemia, any episode of hypoglycemia, over 3 days of hypoglycemia, or severe hypoglycemia (<36 mg/dL). There was no association between hypoglycemia and neurodevelopmental outcome at age 2 years. However, data on the 4.5 year follow-up demonstrated executive function difficulties in those infants suffering more than one episode of hypoglycemia. This was found only with continuous glucose monitoring, not with intermittent sampling.

A unique perinatal cohort reported from Arkansas included 1400 infants tested at 10 years of age who had a

single glucose level in the first hours of life. The single low transitional glucose level was correlated with fourth grade examinations in literacy and mathematics from across the state. A second glucose value was obtained to document glucose values, but there were no further determinations. Glucose levels of interest ranged between below 30 mg/dL and 45 mg/dL. Transient hypoglycemia occurred in 6.4%, 10.3%, and 19.3% of newborn infants with cutoff values of 35, 40, or 45 mg/dL. They found that a single episode of hypoglycemia, defined as under 40 mg/dL that resolved by 3 hours of age, was associated with a 50% reduction in the odds of achieving proficiency in literacy and numeracy at age 10. This group of patients represented all the births during a calendar year, so they were mostly made up of late preterm and term infants. There was little information about the management strategies for hypoglycemia and no reported rates for breastfeeding. It is also possible that the exposure group might have had further exposure to hypoglycemia because only the first two blood glucose levels were measured, and recurrent low glucose levels are common in at-risk infants throughout the first week.

As yet, there is no reason to assume the link between transitional neonatal hypoglycemia and subsequent poor academic performance is causal. It is possible that a brief period of hypoglycemia is a marker for other perinatal issues, perhaps including adverse events during abnormal intrauterine development.

Should we now consider universal screening of all newborns because the Arkansas study suggests transient hypoglycemia may be associated with poorer academic achievement at 10 years? Screening is only justified when you can affect outcome with a screening test. The brief period of hypoglycemia in the Arkansas study was diagnosed at 90 minutes of age, but the actual result wasn't available until 30 minutes after that. The second measurement showing resolution came 70 minutes after the first screen or at 3 hours of age. It is unlikely that any intervention could shorten the exposure to the brief period of hypoglycemia.

Several studies have evaluated whether exogenous glucose or earlier feedings will prevent low glucose concentrations. The studies by Coors et al and Hegarty et al used prophylactic dextrose gel administered to newborn infants at risk for hypoglycemia to increase the initial blood glucose concentrations. In the study by Coors et al, prophylactic dextrose gel did not reduce transient neonatal hypoglycemia or NICU admissions for hypoglycemia. In contrast, the study by Hegarty et al demonstrated that dextrose gel reduced the incidence of hypoglycemia and NICU admissions. A letter to the editor concluded that "providing exogenous glucose to all newborns would apply to the vast majority of term and even many later preterm infants who appropriately do not receive exogenous glucose and normally suckle ad lib. Normal physiologic processes, common throughout the animal kingdom, particularly in mammals, respond to the fall in glucose concentrations that starts almost immediately after birth and produces a robust increase in glycogen breakdown, followed by gluconeogenesis, release of endogenous glucose from the liver, and breakdown of fat to provide alternative fuels to glucose. Providing exogenous glucose would very likely interfere with this normal physiologic response to declining glucose concentrations."

The clinical report from the Committee on the Fetus and Newborn provides a practical guide for the screening and subsequent management of neonatal hypoglycemia in at-risk late preterm (34–$36^{6}/_{7}$ weeks' gestational age) and term infants. The report does not identify any specific value or range of plasma glucose concentrations that potentially could result in brain injury. Instead, it is a pragmatic approach to a controversial issue for which evidence is lacking but guidance is needed. It is clear from the neurologic data that much is yet to be learned and the recommendations are expert opinion based. Providing guidance without all the evidence is implicitly understood with the AAP document.

WHICH INFANTS TO SCREEN

Healthy full-term infants born after an entirely normal pregnancy and delivery and who have no clinical signs do not require screening. Routine measurement of blood glucose concentrations should only be undertaken in infants who have clinical manifestations or who are known to be at risk of a compromised metabolic adaptation. The AAP clinical report was not inclusive of all premature infants and focused only on the late preterm infant. This recommendation assumed that the vast majority of more premature infants would be cared for in intermediate care or in the neonatal intensive care unit, where routine screening is already in place.

Because plasma glucose homeostasis requires gluconeogenesis and ketogenesis to maintain normal rates of fuel use, neonatal hypoglycemia most commonly occurs in infants with impaired gluconeogenesis and/or ketogenesis, which may occur with excessive insulin production, altered counter regulatory hormone production, an inadequate substrate supply, or a disorder of fatty acid oxidation. Neonatal hypoglycemia commonly occurs in infants who are small for gestational age, infants born to mothers who have diabetes, and late preterm infants. Also included are LGA infants because it is difficult to exclude maternal diabetes or maternal hyperglycemia (prediabetes) with standard glucose tolerance tests.

A large number of other maternal and fetal conditions may also place infants at risk of neonatal hypoglycemia (Box 4.2). For the AAP clinical report, it was assumed that clinical signs would be common with these conditions, and it is likely that patients with such conditions would be monitored and that plasma glucose analyses were being performed (Box 4.6).

WHEN TO SCREEN

Plasma glucose should be measured as soon as possible (minutes, not hours) in any infant who manifests clinical signs (Box 4.6) compatible with low blood glucose concentration (i.e., the symptomatic infant). Neonatal glucose

concentrations decrease after birth to as low as 30 mg/dL or less during the first 1 to 2 hours after birth and then increase to higher, more stable concentrations, generally above 45 mg/dL by 12 hours after birth. Values under 40 to 45 mg/dL occur in as many as 5% to 15% of normal newborn infants. Data on the optimal timing and intervals for glucose screening are limited. It seems inappropriate to make early blood glucose measurements on any baby during this immediate fall after delivery, because the normal physiologic decrease cannot be distinguished from the abnormal. Fortunately, even in the absence of any enteral nutrition intake, the blood glucose rises by 3 hours of age. Even in the infant at risk for hypoglycemia, a blood glucose measurement is best avoided during the first 2 hours after birth in the asymptomatic infant. There is the real danger that measurements made at this time are self-fulfilling prophecies. No studies have demonstrated harm from a few hours of asymptomatic low glucose levels during this postnatal period establishing physiologic homeostasis.

Blood glucose concentrations show a cyclic response to an enteral feed, reaching a peak by about an hour after the feed and the nadir just before the next feed is due. Because the purpose of blood glucose monitoring is to identify the lowest blood glucose level, it makes most sense to measure a value immediately before the next feeding.

The AAP guideline recommends the frequency and duration of screening for at-risk groups based on risk factors specific to the individual infant. After 24 hours, repeated screening before feeds should be continued if plasma glucose concentrations remain lower than 45 mg/dL.

LABORATORY MEASUREMENTS OF GLUCOSE

Accurate and rapid measurement of blood glucose concentration is the cornerstone of the management of glycemic status in the neonate. Ideally, it would be rapid, accurate, inexpensive, and require a small volume of blood. Unfortunately, none of the available devices or methods has met all the required attributes for detection of low blood glucose in the neonatal population. When neonatal hypoglycemia is suspected, the plasma or blood glucose must be determined immediately by using one of the laboratory enzymatic methods (glucose oxidase, hexokinase, or dehydrogenase method). Plasma glucose tends to be 10% to 18% higher than whole-blood values because of the higher water content of plasma.

Although a laboratory determination is the most accurate method of measuring the glucose concentration, the results are not available quickly enough for rapid diagnosis of a low blood glucose level, which thereby delays potential interventions and treatments. Bedside reagent test-strip glucose analyzers can be used if the test is performed carefully and the clinician is aware of the limited accuracy of these devices. This bedside or point-of-care (POC) testing is done to obtain an estimate of the glucose concentration quickly and conveniently. Although the results of these tests are used for clinical decisions, there are several pitfalls. At present, there is no POC that is sufficiently reliable and accurate in the low range of blood glucose to allow it to be used as the sole method to screen for hypoglycemia. Test-strip results may vary as much as 10 to 20 mg/dL versus the actual plasma glucose concentration. Unfortunately, this variation is greatest at low blood glucose concentrations.

Because of limitations with rapid bedside methods, the blood or plasma glucose concentration must be confirmed by laboratory testing ordered stat. A long delay in processing the specimen can result in a falsely low concentration because erythrocytes in the sample metabolize the glucose in the plasma. This problem can be avoided by transporting the blood in tubes that contain a glycolytic inhibitor such as fluoride. Treatment of the suspected neonatal hypoglycemia should not be postponed while waiting for laboratory confirmation. However, there is no evidence that such treatment will mitigate neurologic sequelae.

CLINICAL SIGNS OF HYPOGLYCEMIA

The clinical signs of neonatal hypoglycemia are not specific and include a wide range of local or generalized manifestations that are common in sick neonates (Box 4.6). The signs and symptoms of isolated hypoglycemia can be viewed as systemic manifestations of glucopenia (e.g., episodes of cyanosis, apnea, irritability, poor sucking or feeding,) and/or manifestations of central nervous system glucose deficiency (neuroglycopenia; e.g., changes in level of consciousness, tremors, irritability, lethargy, seizures, exaggerated Moro reflex, coma). The manifestations of neuroglycopenia include the full spectrum of acute encephalopathy. Coma and seizures may occur with prolonged neonatal hypoglycemia (plasma or blood glucose concentrations lower than 10 mg/dL range) and repetitive hypoglycemia.

Because avoidance and treatment of cerebral energy deficiency is the principal concern, greatest attention should be paid to neurologic signs. The clinical manifestations should subside within minutes to hours in response to adequate treatment with intravenous glucose if hypoglycemia alone is responsible. Cornblath and colleagues have suggested that the Whipple triad be fulfilled: (1) a low blood glucose concentration, (2) signs consistent with neonatal hypoglycemia, and (3) resolution of signs and symptoms after restoring blood glucose concentrations to normal values.

PERSISTENT HYPOGLYCEMIC DISORDERS

Some neonates can be identified by various clinical features as being high risk for severe hypoglycemia during the first 48 hours of life. Other infants are at risk for persistent hypoglycemia beyond 48 hours of life (Box 4.4). These include not only the rare infants with genetic hypoglycemic disorders, such as congenital hyperinsulinism or hypopituitarism, but also those with relatively more common prolonged neonatal hyperinsulinism (also referred to as perinatal stress hyperinsulinism) associated with birth asphyxia, intrauterine

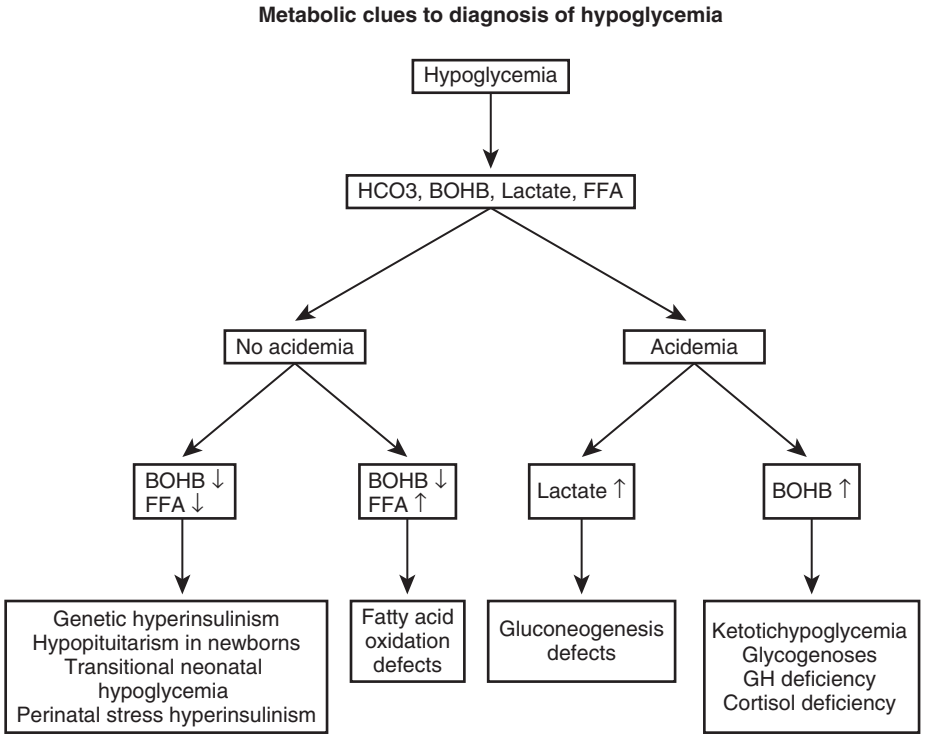

Fig. 4.9 Algorithm showing how the major categories of hypoglycemia may be determined with information from the critical sample. *BOHB,* Beta-hydroxybutyrate; *FFA,* free fatty acids; *GH,* growth hormone. (From Thornton PS, Stanley CA, DeLeon DD, et al: Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in neonates, infants, and children, *J Pediatr* 167:238–245, 2015.)

growth restriction, or born to women with toxemia of pregnancy. Fig. 4.9 provides an algorithm showing how the major categories of persistent hypoglycemic disorders may be determined from the critical sample of beta-hydroxybutyrate, free fatty acids, and growth hormone.

To increase the detection of these persistent hypoglycemic syndromes, it is prudent to use both the AAP and PES recommendations. It makes sense to use the AAP algorithm for the first 24 hours and then use over 45 mg/dL as an operational threshold for 24 to 48 hours. Discharge should be delayed for infants who required intravenous fluids for symptomatic or asymptomatic low glucose levels or those with borderline low glucose levels after 72 hours using the PES recommendations for over 65 to 70 mg/dL through several normal feed–fast cycles. More data on the frequency and success of diagnosing persistent hypoglycemia will be necessary to support this strategy.

DEXTROSE GEL FOR TREATMENT OF HYPOGLYCEMIA

In a secondary analysis of the Sugar Babies Study, infants were randomized to 40% dextrose gel or placebo for a low blood glucose value. After subjects received the gel, feeding was attempted either by direct breastfeeding, expressed breast milk, formula, or a combination of these based on maternal preference. The response to treatment with buccal gel (dextrose or placebo) and feeding was assessed by measuring the glucose concentration 30 minutes after the gel was administered.

The mean increase in glucose concentration for all hypoglycemic episodes was 11.7 mg/dL. Infants who received dextrose gel had a 3.0 mg/dL larger increase in glucose concentration than those who received placebo gel. Formula feeding, whether combined with direct breastfeeding or expressed breast milk or not, was associated with a larger increase in glucose concentration (3.8 mg/dL) compared with infants who did not receive formula. Furthermore, the response to dextrose gel was independent of the formula response, suggesting an "additive" rather than "synergistic" effect of formula feeding versus dextrose gel.

A Cochrane review, including two trials with 312 infants, concluded that treatment with 40% dextrose gel reduces the incidence of mother–infant separation for treatment of hypoglycemia and increases the likelihood of full breastfeeding after discharge compared with the placebo gel. No evidence suggests occurrence of adverse effects during neonatal period or at 2 years of age. Oral dextrose gel should be considered first line treatment of infants with neonatal hypoglycemia.

CONCLUSION

There is need for rigorous long-term studies comparing thresholds of treatment to determine whether outcomes can be affected by early and aggressive treatment of transitional associated hypoglycemia. In addition, the levels that are treated after 4 hours in asymptomatic infants need similar study. Until these studies are available, expert opinion is relied on to interpret evidence, which is lacking.

Current evidence does not appear to support a specific concentration of glucose in the neonate that identifies neuroglycopenia. We are unable to predict the acute or chronic irreversible neurologic damage will result if this critical level is reached. Dextrose gel may help keep mothers and infants together, breastfeeding, and out of the NICU.

As history has shown, every time there are more answers in neonatal hypoglycemia they seem to raise more questions when it comes to the management of neonatal hypoglycemia.

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Abstract: Low blood glucose levels are one of the most frequently encountered issues in the newborn nursery. The blood levels upon which we base our decision making are more a matter of expert opinion than being based on solid evidence. The data needed to establish consensus on low blood glucose levels do not exist yet. The American Academy of Pediatrics Committee on Fetus and Newborn and the Pediatric Endocrine Society (PES) have offered advice on management and also for the PES an appeal for trying to diagnose persistent hypoglycemic syndromes before discharge. Postnatal glucose homeostasis and transitional neonatal hyperinsulinemia has advanced our understanding of metabolic and hormonal responses to various levels of plasma glucose. This unique first 48 hours occurs in all mammals not just humans and controversy exists about whether it is physiologic and affords benefits to the newborn. However, hypoglycemia represents an imbalance between glucose supply and utilization and may result from different regulatory mechanisms. It is certain that persistent low glucose levels that lead to neurologic symptoms are morbid and must be prevented and/or treated emergently. A new therapy using dextrose gel to treat low blood glucose level appears promising and the use of continuous glucose monitoring may offer more insight into the undiagnosed episodes of hypoglycemia that intermittent blood sampling misses.

Keywords: Hypoglycemia, Transitional Neonatal Hyperinsulinemia, Operational Thresholds, Persistent Hypoglycemia, Dextrose Gel, Continuos glucose monitoring