CHAPTER 4

GLUCOSE METABOLISM

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CASE STUDY 1

A 30-year-old primigravida after an uncomplicated pregnancy is admitted in labor at 38 weeks' gestation. The perinatal screening tests are negative including a negative screen for group B Streptococcus *(GBS) at 36 weeks of gestation. Membranes rupture occurred 2 hours prior to vaginal delivery. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The male infant weighs 3200 grams. The mother has planned to exclusively breastfeed the baby and she begins in the delivery room with what is described as a "successful" first feed. Shortly thereafter, mother and baby are transferred to a postpartum room.*

Prior to the baby being breastfed at 8 hours of age, the nurse on a routine assessment thinks the baby has slight tremors and she performs a point-of-care 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 advises that after this feeding the mother should supplement the infant with one ounce of a term 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 nurse calls you at home and discusses the findings and what is going on and that the mother is disappointed about having to give formula supplement to her baby.

- *Is the nurse offering correct advice to this mother?*
- *Do you have orders for screening and management of glucose levels for the well baby?*

You have your smart phone with you and you pull up the "Glucose App, Sugar Wheel" (Figure 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.

EXERCISE 1

QUESTIONS

1. Should this term, appropriate for gestational age breastfeeding infant been screened at all?
2. Is this infant symptomatic? Because the glucose value was <40 mg/dL, should the infant have received intravenous glucose?
3. Should a plasma glucose concentration have been sent to the lab?
4. Should the infant simply have been left to continue breastfeeding?
5. Do infants that are exclusively breastfed tend to have lower plasma glucose concentrations than those fed infant formulas?

ANSWERS

1. Yes, if the tremors were really symptoms.
2. The tremors may not have been related to hypoglycemia because the level is not particularly low.
3. Always send confirmatory value to lab for plasma glucose if you are concerned about symptoms.
4. Yes, if the symptoms are really not symptoms or related to the plasma glucose level, which is not low.
5. Breastfed infants probably do have lower plasma glucose levels than formula fed.

CASE STUDY 1 (continued)

This case demonstrates a few of the issues that we will consider in the chapter. Cornblath and Reisner established (nearly 50 years ago) that neonatal hypoglycemia was a significant cause of neonatal mortality and morbidity, yet the definition and management of neonatal hypoglycemia have remained unclear. We will examine the controversies and discuss what constitutes clinically significant

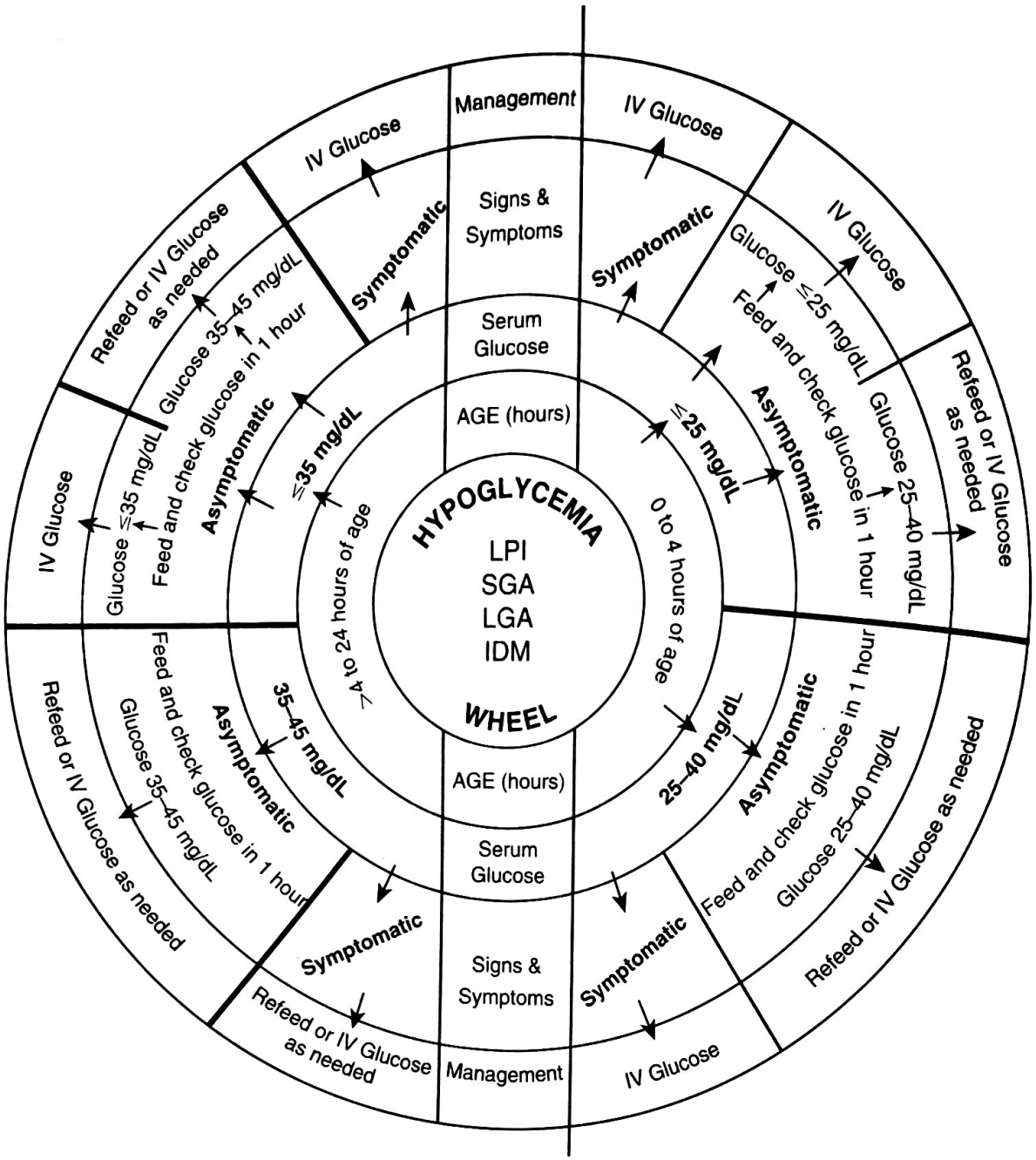

FIGURE 4-1 ■ Sugar Wheel nomogram for postnatal glucose homeostasis.

hypoglycemia, who should be screened and when, laboratory methods, and the relationship between "low" plasma glucose concentrations and long-term neurologic outcomes.

INTRODUCTION

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?

More than a decade ago, Cornblath and colleagues summarized the contemporary state of knowledge relating to neonatal hypoglycemia by stating the following: "Unfortunately, untoward long-term outcomes in infants with one or two low blood glucose levels have become grounds for litigation and for alleged malpractice, even though the causative relationship between the two is tenuous at best. . . . The definition of clinically significant hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology."

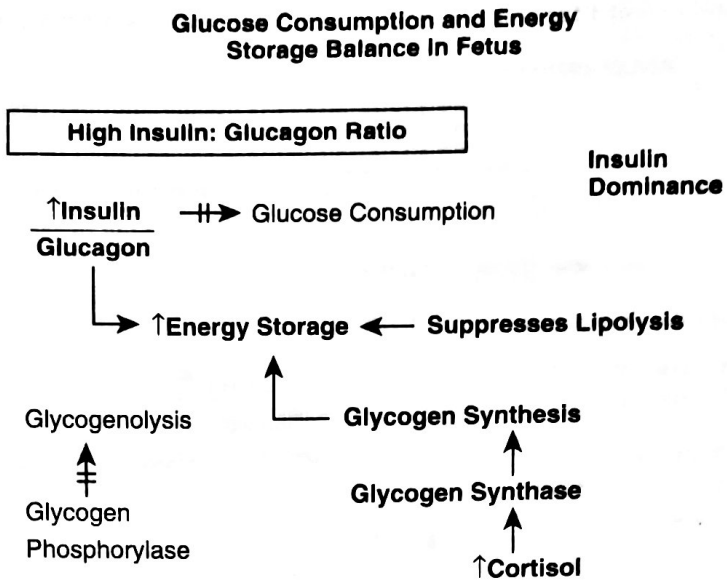

FIGURE 4-2 ■ Fetal maintenance of anabolic state promoting energy storage.

Four years ago a workshop report from the Eunice Kennedy Shriver National Institute of Child Health and Human Development was published in the *Journal of Pediatrics*, after a group of experts from around the world was assembled in Washington, D.C. to focus on gaps in knowledge and suggest research needs for understanding and treating neonatal hypoglycemia. Conclusions from the workshop included: "There is no evidence-based study to identify any specific plasma glucose concentration (or range of glucose values) to define pathologic hypoglycemia." "Monitoring for and prevention and treatment of neonatal hypoglycemia remain largely empirical." Finally the report concludes, "at present data are insufficient to produce definitive guidelines." At the same time as this conference was taking place, the Committee on Fetus and Newborn for the American Academy of Pediatrics was working on a clinical report to provide guidance and an algorithm for the screening and subsequent management of neonatal hypoglycemia.

GLUCOSE HOMEOSTASIS

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 that the transition may 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 (Figure 4-2). 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 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 (Figure 4-2).

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 (Figure 4-3). Catecholamine concentrations increase immediately after delivery and this stimulates glucagon secretion. Therefore, there is a decrease in the insulin/glucagon ratio. This ratio is important because it drives events in utero and in transition that explain fetal preparedness for transition and the postnatal adaptation and glucose homeostasis.

When glycogen synthase is inactivated and glycogen phosphorylase is activated, this leads to

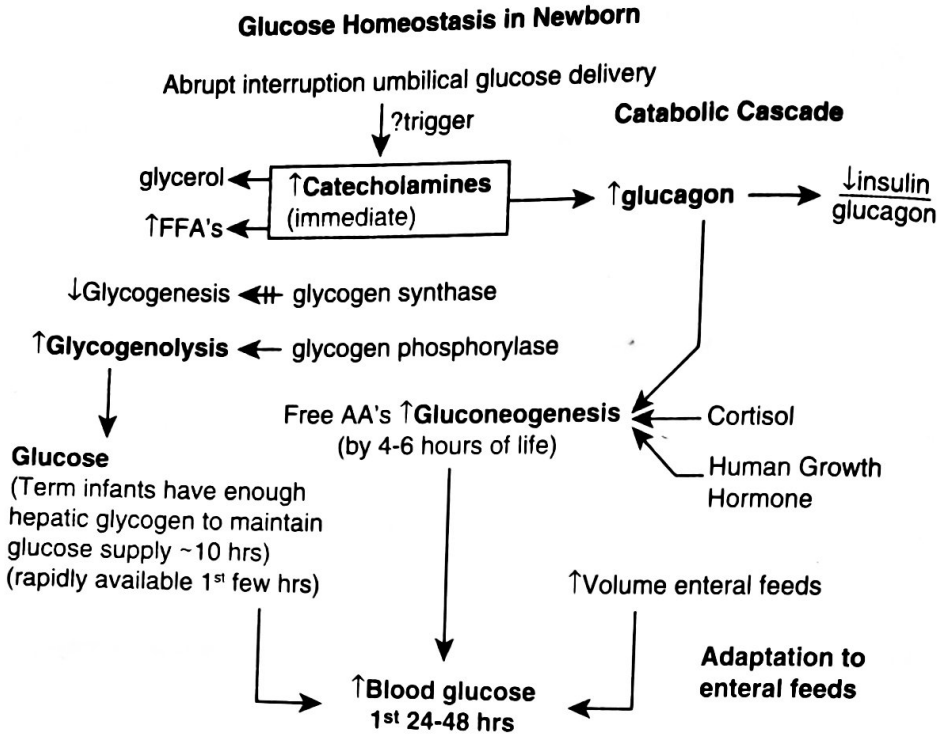

FIGURE 4-3 ■ Adaptations around delivery and over the first 24 hours of life to establish postnatal glucose homeostasis.

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 the 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 come into play to maintain glucose homeostasis (Figure 4-3).

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 that lead to the availability of glycerol and amino acids from the circulation. 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 that there will be neonatal hypoglycemia.

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 when these infants were commonly starved the first few days of life. These low values are no longer observed in preterm infants because of early intravenous therapy and/or enteral feedings. In fact, the preterm infant has a significantly greater fall in glucose within the first few hours after birth 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 owing to immaturity of the enzymatic pathways.

CASE STUDY 2

A term appropriate for gestational age (AGA) male infant was born after an uneventful pregnancy to a 30-year-old gravida 2 woman. The mother had no evidence of hyperglycemia and no chronic diseases. Apgar scores were 5, 7, and 8 at 1, 5, and 10 minutes, respectively. The baby received blow-by oxygen in the delivery room because of cyanosis. At approximately 1 hour of age, a bedside glucose determination was obtained; the value was 27 mg/dL. The infant then received his first feeding of formula after a plasma glucose level was sent to the

lab. The plasma glucose concentration run by the lab was 35 mg/dL and the repeat bedside glucose 1 hour after the feeding was 36 mg/dL.

EXERCISE 2

QUESTIONS

1. Should this baby have received the initial screening bedside glucose at 1 hour of age?
2. What is the significance of 27 mg/dL at 1 hour of age prior to feeding?
3. Why does the plasma glucose concentration of 35 mg/dL (from the laboratory) differ from the bedside screen, which was 27 mg/dL?
4. The repeat bedside glucose is 36 mg/dL at 2 hours of age after a feeding of formula. Is that level still actionable?

ANSWERS

1. Cyanosis at delivery is very unlikely due to these levels of plasma glucose. It was the reason the infant was screened.
2. The bedside screen of 27 mg/dL is typical of the nadir during metabolic transition (the actual plasma value was 35 mg/dL).
3. Bedside screening values are not as accurate as plasma levels, particularly at low levels of glucose.
4. The repeat level of 35 mg/dL is still actionable. However, this infant probably should not have been screened and was asymptomatic and well.

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 to 1.4 mmol/L). The abnormal signs cleared quickly after increasing the blood glucose concentration to (>40 mg/dL, 2.2 mmol/L). Now 60 years later, after hypoglycemia was first described and "40" mg/dL became a "classic" standard for defining hypoglycemia, our understanding of the metabolic disturbances and genetic defects underlying aberrations in postnatal glucose homeostasis has increased dramatically. However, this growth of knowledge, if anything, has led us further from what we need to know about

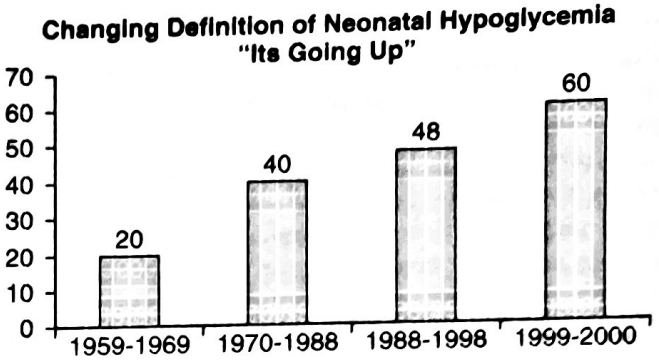

FIGURE 4-4 ■ Plasma glucose concentrations considered representing hypoglycemia over the last 40 years.

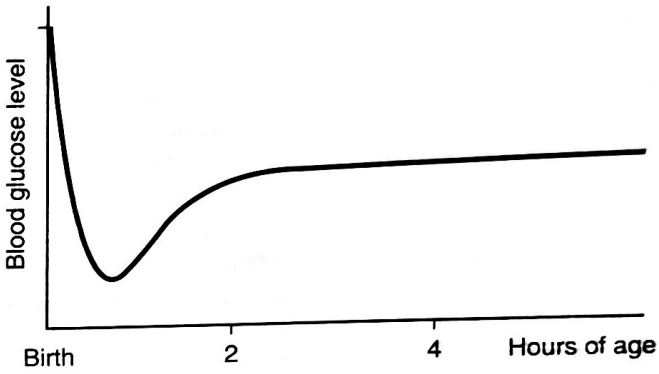

FIGURE 4-5 ■ Blood glucose concentration transition from fetus to neonatal over the first hours of life. (From Srinivasan G, Pildes RS, Cattaman G: Plasma glucose values in normal neonates: a new look, *J Pediatr* 109[1]:114-117, 1986.)

blood glucose concentrations in the newborn: "How low is too low?"

In a review of current textbooks, there is no consensus for the definition of hypoglycemia; values range from 18 mg/dL (1 mmol/L) to 70 to 100 mg/dL (3.8 to 5.5 mmol/L). It is interesting to note that the definition of neonatal hypoglycemia has gone up decade by decade over the last forty years (Figure 4-4); however, the higher blood glucose values that have been proposed are without scientific justification. The easiest diagnosis may be the situation in which the symptoms associated with a low blood sugar resolve when the blood sugar concentration is increased. Apart from this clinical situation, the diagnosis of hypoglycemia is much more complex.

The blood glucose concentrations during the immediate postnatal period are important to understand to determine what may or may not constitute a low blood sugar concentration. At birth, the blood glucose concentration in the umbilical venous blood is 70% to 90% of that in the maternal venous blood. Blood glucose concentration falls rapidly after birth, reaching a nadir by 1 hour of age or so and then rises to stabilize by 3 hours of age despite the absence

of any nutritional support (Figure 4-5). During this period, plasma insulin levels are falling as glucagon levels surge. This surge of glucagon combined with low insulin levels is the key hormonal adaptation in the newborn infant that leads to mobilization of glycogen. Plasma glucose concentrations are lowest at 1 to 2 hours of age and may reach a nadir as low as approximately 30 mg/dL (1.8 mmol/L), or even lower (Figure 4-6), after which time the infant's normal physiologic responses increase the glucose concentrations to values greater than 45 mg/dL (2.5 mmol/L), which are maintained over the first days of life (Figure 4-6).

Several approaches have been taken to determine normal reference ranges for blood glucose concentrations in normal newborns. The first was to sample umbilical venous blood at various times during gestation and establish reference ranges for blood glucose concentrations for the normal fetus and then apply these glucose concentrations to the newborn. This method demonstrated a range of 54 to 90 mg/dL with a mean concentration of 70 mg/dL. Another approach was to measure the glucose values in full-term, appropriately grown newborn infants without any prenatal or neonatal complications over the first few hours. These values are shown in Figures 4-5 and 4-6.

In using these approaches one can arrive at a statistical definition of hypoglycemia in the normal term after 12 hours of life of 36 to 45 mg/dL. However, the literature does not provide a consensus for a threshold blood or plasma glucose concentration that specifically defines hypoglycemia or when and how much treatment should be provided. Attempts have also been made to identify the threshold blood glucose concentration in which there is substantial likelihood of functional impairment, particularly the brain. These methods can be categorized into five approaches: epidemiologic, clinical, metabolic-endocrine, neurophysiologic, and neurodevelopmental.

The epidemiologic approach simply defines blood concentrations in a cohort of healthy infants, and then uses an empirically derived cut-off such as <2 standard deviations below the mean. Any single value is unlikely to represent a threshold of abnormality, because the data represents a continuum from normal. Most important is that a statistical abnormality does not imply a biologic impairment. This method shows the vast majority have blood glucose concentrations >40 mg/dL.

The clinical approach is based on the importance of glucose levels when signs of hypoglycemia appear. However, jitteriness is just as likely

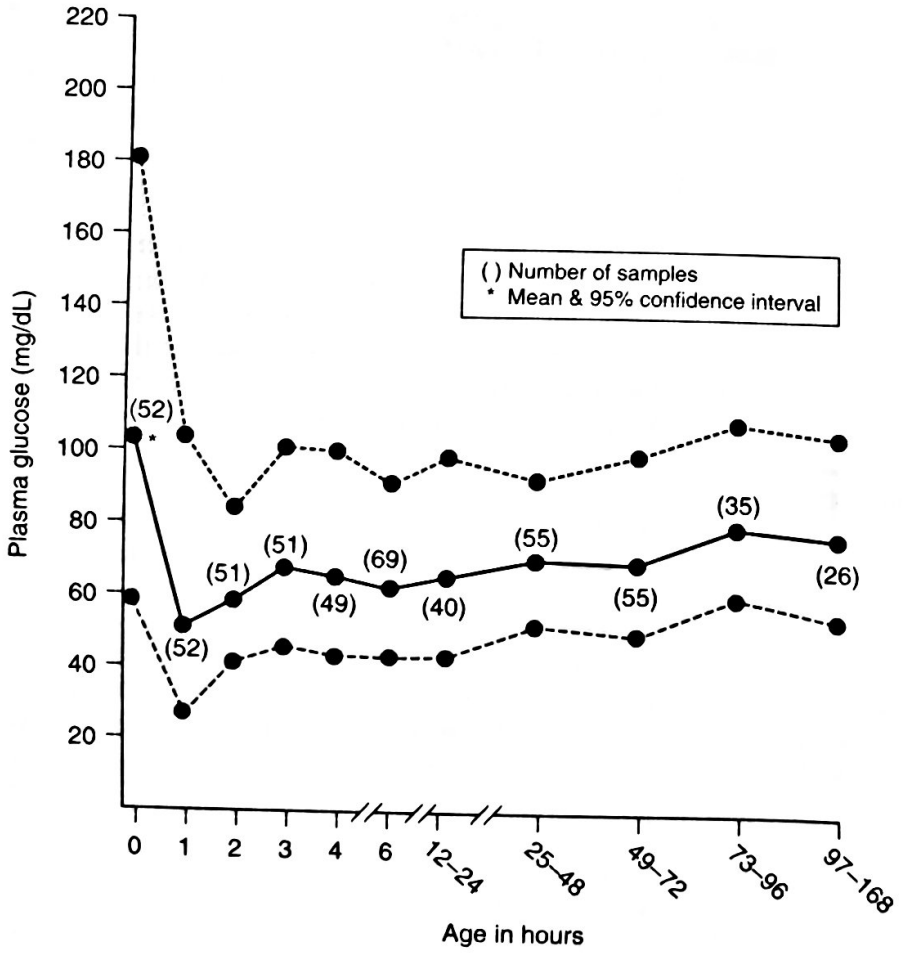

FIGURE 4-6 ■ Plasma glucose concentrations in full-term, appropriately grown newborns without any prenatal or neonatal complications. (From Srinivasan G, Pildes RS, Cattaman G: Plasma glucose values in normal neonates: a new look, *J Pediatr* 109[1]:115, 1986)

among normoglycemic infants and those with a variety of other conditions. Also, equally low blood glucose levels are found in infants with no signs ("asymptomatic hypoglycemia"). This is often seen in the first few hours after birth when fuels other than glucose are providing neural energy and the brain is protected despite the "low plasma glucose screen." Therefore, the presence or absence of signs and symptoms cannot be used to discriminate between normal and abnormal blood glucose values.

The metabolic-endocrine approach is not practical and needs more data. The premise is that the concentration of glucose at which metabolic counterregulation occurs can be used to define a "safe" lower limit for blood glucose concentration. Premature infants are unable to mount a mature counterregulatory response to low blood glucose levels compared to term infants, thus making them more vulnerable during periods of insufficient fuel.

Similarly, the neurophysiologic approach has attempted to measure neurophysiologic changes in relation to various blood glucose concentrations. Studies use somatosensory evoked potentials. The studies have had small numbers and some studies have failed to show effects of hypoglycemia on evoked responses. Changes in cerebral blood flow with very low blood glucose concentrations have been studied in preterm infants. However, the practicality of this technology and application remain unclear.

The neurodevelopmental approach has taken on the most significance for many investigators to define significant hypoglycemia and also is pivotal in the Canadian Pediatric Statement and algorithm on screening and management of hypoglycemia. An important and very influential article from the United Kingdom published in 1988 by Lucas and colleagues opened with "there has been considerable debate over what should be chosen as a safe lower limit for blood glucose concentration in the neonatal period." The article provided data on 661 infants who weighed <1850 g at birth, and from the data the authors concluded that "moderate hypoglycemia may have serious neurodevelopmental consequences, and reappraisal of current management is urgently required." They used statistical strategies to analyze for a threshold value that reliably predicted an adverse outcome. They suggested that a glucose concentration <47 mg/dL (<2.5 mmol/L) offered the greatest predictive power. They found that the number of days that these infants experienced moderate hypoglycemia was strongly related to reduced scores for mental and motor development at 18 months corrected age, even after adjustment for a wide range of factors known to influence development. However, the monitoring of blood glucose was not standardized; sicker infants had more frequent blood glucose determinations. The fact that hypoglycemia was not a primary focus of this prospective controlled feeding study is apparent from the observation that some infants were permitted to have plasma glucose values <20 mg/dL (<1.1 mmol/L) for as long as 3 to 7 days without intervention. In addition, the glucose value reported and used in their analyses for prognosis was the first one obtained each day and the number of days <47 mg/dL were usually not consecutive.

The adjustment for confounding variables and the large sample size were positive aspects of this study. Therefore for high-risk infants with birthweight <1850 g, a first glucose value of <47 mg/dL on 5 or more days correlated positively with abnormal neurologic and developmental outcomes at 18 months of age. However, by 7.5 to 8 years of age, only deficiencies in arithmetic and motor test scores were present. This suggested the findings at 18 months were not permanent. Thus, doubt was cast on the importance of a threshold value <47 mg/dL as a marker for neuroglycopenia or, alternatively, it suggests that early adversity may be attenuated by later environmental factors.

A second retrospective study gained importance in trying to define a "threshold" level for increased risk of brain injury. The study included small for gestational age preterm infants <32 weeks' gestation, the majority of whom had symmetric growth restriction including head circumference. They reported 73% of these infants had hypoglycemia (i.e., <47 mg/dL), and that recurrent episodes of hypoglycemia strongly correlated with physical growth deficits and persistent neurodevelopmental delays. In this study, the initial bedside screen was not confirmed with a laboratory plasma glucose in many of the infants.

A prospective controlled clinical trial with a strict protocol for measuring frequent blood glucose levels at specific times and with explicit indications is necessary. The approach that links statistically based hypoglycemia with outcome measures like abnormal neuromotor and intellectual performance at 18 months of age or older cannot be validated without this prospective study.

Recently another group in the United Kingdom, Tin and colleagues, completed a prospective study that evaluated neurodevelopmental outcomes at 2 and 15 years later for preterm infants who had a low blood glucose level during the first 10 days of life. This study was designed to test the hypothesis that recurrent low blood glucose levels <47 mg/dL, even in the absence of any suggestive clinical signs, can harm a preterm infant's long-term development.

All children born <32 weeks in the north of England in 1990 to 1991 had laboratory blood glucose levels measured daily for the first 10 days of life. Forty-seven of the 566 who survived to 2 years had a blood glucose level <47 mg/dL for more than 3 days. All were matched with hypoglycemia-free controls matched for appropriate variables. No differences in developmental progress or physical disability were detected at 2 years of age.

The families were seen again when the children were 15 years old, and 38 (81%) of the original cohort and matched controls were nearly identical for full scale IQ. Even children who had a level <47 mg/dL for >4 days and another group <36 mg/dL on 3 different days did not alter these results. Tin concluded "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."

Tin's study doesn't imply that low blood glucose concentrations cannot be damaging in the preterm infant even in the absence of overt recognizable signs. However, the data suggest that the danger threshold must be lower than many had come to think it was.

A recent analysis of all 18 reported eligible studies through 2005 on neonatal hypoglycemia and subsequent neurodevelopmental outcomes concluded that the overall methodologic quality was poor in 16 and high in two studies. None of the studies provided a valid estimate of the effect of neonatal hypoglycemia on neurodevelopmental outcomes. They developed a proposal for a well-designed prospective study, which the second UK study by Tin and colleagues represents.

Rozance and Hay, reviewing features associated with adverse outcomes in infants with hypoglycemia, conclude that attributing long-term neurologic impairment to neonatal hypoglycemia is difficult and controversial. They also suggest there are no definitive studies that have been able to address this issue. Conditions to consider when entertaining this possibility are listed in Box 4-1.

CASE STUDY 3

A term male infant is born to a 21-year-old primigravida who had no prenatal care. Because of failure to progress, a cesarean section was performed. Apgar scores were 6 and 7 at 1 and 5 minutes, respectively. The infant weighed 4550 grams and the length and head circumference both plotted out at the 50th percentile on the fetal growth curve. At 6 hours of age, the infant appears lethargic, feeding poorly at the breast, and jittery. A bedside glucose determination was performed and the reading was 10 mg/dL. A plasma glucose was sent to the laboratory.

EXERCISE 3

QUESTIONS

1. When should this infant with macrosomia and no prenatal care be screened for neonatal hypoglycemia?
2. Do you consider this infant asymptomatic with a low blood glucose concentration, or a symptomatic infant with a low blood glucose concentration?

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 to 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 vs. 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.*

3. Would you immediately feed this infant or would you be providing intravenous glucose by mini-bolus and/or glucose infusion?

ANSWERS

1. This infant with macrosomia should have been screened 30 minutes after the first feeding, which should have taken place by 1 hour of age.
2. This infant has signs that can be consistent with hypoglycemia.
3. The infant that is symptomatic with hypoglycemia and demonstrates a low bedside glucose and/or plasma screen should be treated immediately.

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 it not diagnostic of a disease. One uses available clinical and experimental data for these infants using conservative estimates for designating 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 or less for the healthy full-term or late preterm (34 to 37 weeks' gestation) formula-fed infant. 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 to 2.8 mmol/L) or higher in a sick, low birth weight, or premature infant 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 neurologic injury. 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 be 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

BOX 4-2 Pathogenesis of Hypoglycemia in Neonates

EXCESS UTILIZATION

Hyperinsulinism: IDM, erythroblastosis, LGA, SGA, or islet cell or other endocrine pathology

Increased calorie expenditure for thermoregulation in LBW and SGA infants

Increased calorie expenditure owing to excess muscle activity: increased work of breathing in respiratory distress, drug withdrawal, CNS irritability

Circulatory or respiratory diseases that shift energy metabolism from aerobic to anaerobic pathways: hypoxemia, hypotension, hypoventilation, septic shock

Relative excess of glucose-dependent tissues: high brain-to-liver ratio in SGA infants

Inborn errors of metabolism resulting in inadequate glucose-sparing substrates: free fatty acids, ketones, glycerol, amino acids, lactate

Acute brain injury causing increased brain glucose utilization: seizures, intoxication, meningitis, encephalitis, or hypermetabolism following acute brain injury (hypoxia-ischemia, trauma, hemorrhage)

INADEQUATE PRODUCTION OR SUBSTRATE DELIVERY

Inadequate or delayed feedings or parenteral delivery of calories

Aberrant hormonal regulation of glucose or lipid metabolism: hypothalamic, pituitary, and peripheral endocrine disorders

Transient developmental immaturity of critical metabolic pathways reducing endogenous production of glucose and/or other substrates

Deficient metabolic reserves of precursors or glucose-sparing substrates

Deficient brain glucose transporters: posthypoxia-ischemia, inherited glucose transporter defects

Suppression of gluconeogenesis, glycogenolysis, and hepatic glucose release by inappropriately high circulating insulin levels in conditions associated with hyperinsulinism.

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.*

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 for such injury. He emphasized 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 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."

PHYSIOLOGIC RESPONSES TO HYPOGLYCEMIA AND BRAIN INJURY

There is no definitive study of glucose insufficiency in human infants in relation to hypoglycemia and acute neuronal injury. 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, 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 exam assessing for signs and symptoms of hypoglycemia and particularly neurologic abnormalities may help distinguish those infants with low blood glucose concentrations who are adequately compensating. Figure 4-7 shows the many factors (neuronal fuel economy) that must be considered in evaluating the infant with a low blood glucose concentration.

Some studies have shown increased cerebral blood flow in the hypoglycemic infant compared to normal, healthy euglycemic infants; after treatment the cerebral blood flow returned to normal in 30 minutes, as did epinephrine levels, which had risen as well with hypoglycemia. However, studies have not shown a change in cerebral rate of glucose utilization in relation to the change in cerebral blood flow.

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 and metabolism by 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 increased to a maximum concentration on days 2 and 3. Additionally, the ketone bodies increased further

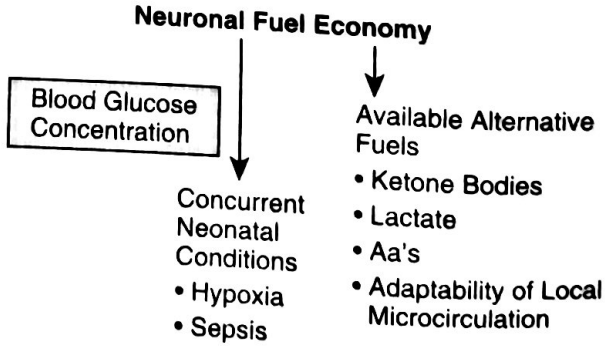

FIGURE 4-7 ■ Factors that play a role in energy available for the central nervous system including blood glucose concentrations.

when the glucose concentration in the blood was low. However, preterm infants did 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; however, 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.

CASE STUDY 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 follow the feeding?
3. Do breastfeeding babies have higher ketone levels and lower blood glucose levels than formula-fed infants?

ANSWERS

1. This infant does not meet any of the risk categories for screening and management of postnatal glucose homeostasis.
2. Glucose screens during the first 4 hours of life are taken 30 minutes after feedings. Thereafter, screens precede feedings for optimal management.
3. Breastfeeding infants are believed to have higher ketone levels, the principal alternate metabolic fuel for the brain, thus sparing glucose.

BREASTFEEDING

In most term infants who are formula fed, the plasma glucose concentration exceeds 40 mg/dL by 6 to 12 hours of postnatal age. Infants who are exclusively breastfed tend to have lower blood glucose concentrations that those fed formula. One study noted that nearly 50% of breastfed infants had blood glucose levels remaining below 36 mg/dL during the first 24 hours after delivery. Other studies show a very wide range of glucose concentrations during the first 72 hours with lower limits at 23 mg/dL in healthy breastfed infants (Table 4-1). Furthermore, breastfed infants tend to have higher ketone concentrations, the principal

TABLE 4-1 Plasma Glucose Concentrations (mmol/L) in Term, Appropriate Size for Gestation, Breastfed Infants at Four Different Ages

Age (hr)	Mean	Median	Interquartile Range	Range
3	54 (19)	50.4	25.2-149.4	41.4-59.4
6	53.1 (13.5)	50.4	28.8-97.2	43.5-59.4
24	52.02 (14.2)	52.2	23.4-136.8	46.8-59.4
72	54 (14.2)	50.4	25.2-127.8	46.8-59.4

Repeated analysis of variance, $p = 0.9$

From Wight N: Hypoglycemia in breastfed neonates, Breastfeed Med *1(4):253, 2006.*

alternate metabolic fuel for the brain. Therefore, studies indicate that breastfed term infants have lower blood glucose concentrations and higher levels of ketone bodies than formula-fed infants. Data extended out to 1 week of age showed that breastfed infants still had significantly lower mean blood glucose levels (range 27 to 95 mg/dL) with mean of 58 mg/dL versus formula-fed of the same age at (range 45 to 111 mg/dL) and mean of 72 mg/dL. A unique observation is that the breastfed infants losing the most weight postnatally had the highest ketone body concentrations. This suggests alternate fuel neuroprotection as a normal adaptive response to a transiently low nutrient intake with modest breastfeeding volumes as they increase the first week of life. For the breastfed infant, the only correlation with glucose concentration was the interval between feeds. This emphasizes the need for lactation support, monitoring, and frequent on-demand nursing.

Wight promotes early and exclusive breastfeeding as meeting the nutritional needs of the healthy, term infant and that these infants do not develop symptomatic hypoglycemia simply as a result of underfeeding. She advises against routine supplementation of these healthy infants with water, glucose water, or formula because these may interfere with the establishment of normal breastfeeding.

Healthy term infants should initiate breastfeeding within 30 to 60 minutes of life and continue on demand, recognizing that crying is a very late sign of hunger. Frequent feedings are best 10 to 12 times per 24 hours, which also helps prevent hyperbilirubinemia in the first few days after birth.

If a breastfed term infant meets criteria for glucose screening it should not preclude early initiation of breastfeeding. The infant can be monitored and further clinical decisions should be based on subsequent glucose monitoring and clinical exam. If such an infant does develop hypoglycemia, it is important to reassure the mother that there is nothing wrong with her breast milk and that supplementation or whatever treatment is necessary is usually temporary and the intent is not to jeopardize breastfeeding her infant. In some cases, the mother may want to express or pump milk that is then fed to her infant. It is important to maintain her milk supply until the baby is back to latching and suckling well. Trying to keep the baby on the breast or returning to the breast as soon as is safely possible is important to maintain breastfeeding for mother and baby.

POSTNATAL GLUCOSE HOMEOSTASIS IN LATE-PRETERM AND TERM INFANTS

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 to 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. Recommendations include: which infants to screen, when to screen them, laboratory data, clinical signs, and finally management.

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 concentration should only be undertaken in infants who have clinical manifestations or who are known to be at risk of compromised metabolic adaptation. The AAP clinical report was not inclusive of all premature infants and focused only on the late preterm infant. This was based on the assumption 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 counterregulatory 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. Included as well are large for gestational age infants because it is difficult to exclude maternal diabetes or maternal hyperglycemia (prediabetes) with standard-glucose tolerance tests.

A large number of additional 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

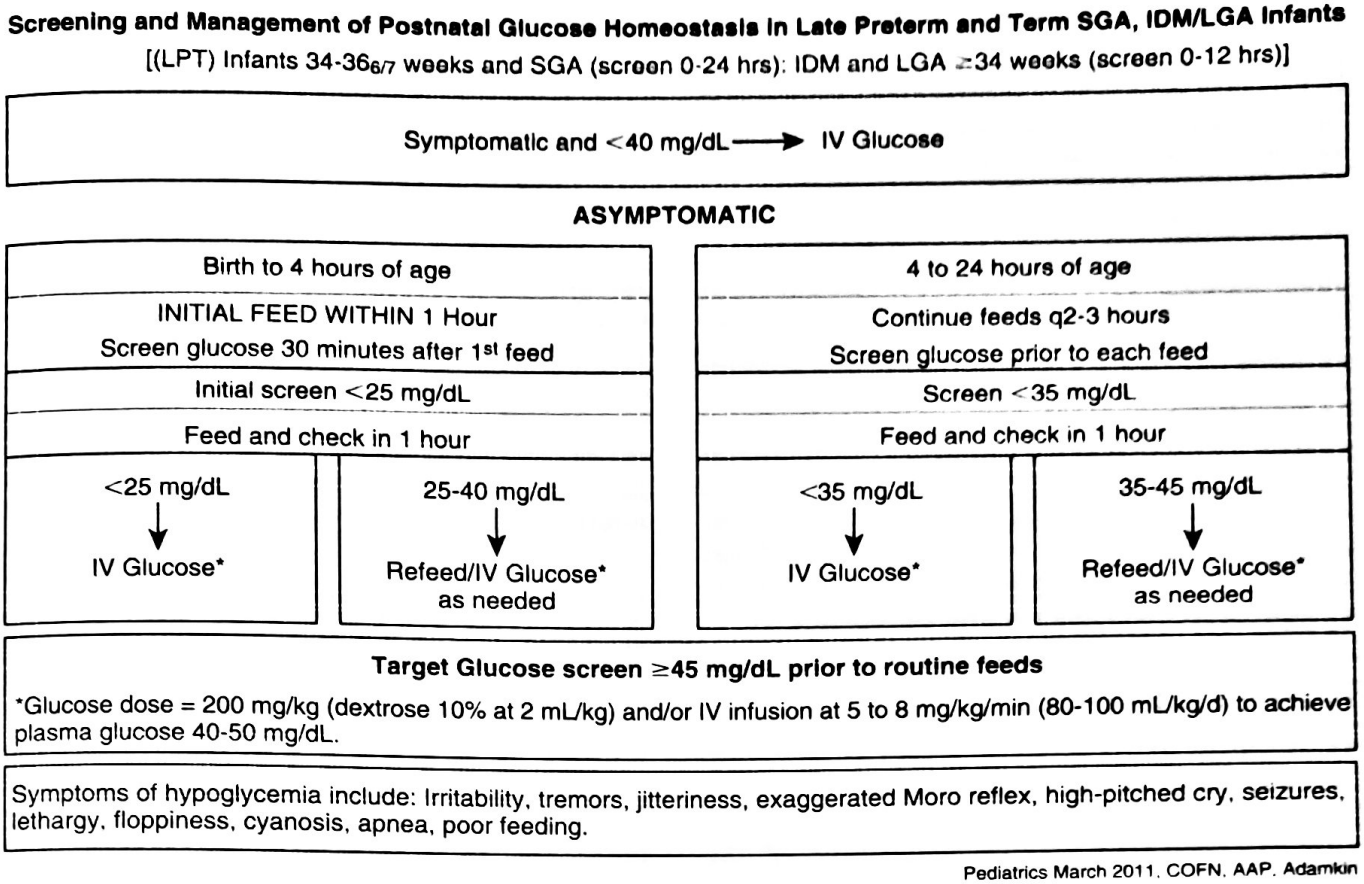

FIGURE 4-8 ■ Screening and management of postnatal glucose homeostasis from the AAP Committee on Fetus and Newborn. (From Adamkin DH: Postnatal glucose homeostasis in late-preterm and term infants, *Pediatrics* 127[2]:576, 2011)

is likely that patients with such conditions would be monitored and that plasma glucose analyses were being performed. Therefore for practicality, "at risk" in the management approach outlined in Figure 4-8 includes only infants who are small for gestational age, infants who are large for gestational age, infants who were born to mothers with diabetes, and late preterm infants.

WHEN TO SCREEN

Plasma glucose should be measured as soon as possible (minutes, not hours) in any infant who manifests clinical signs (Box 4-3, Figure 4-8) 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 <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 because the normal 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 "at-risk" infant for hypoglycemia, blood glucose measurement is best avoided during the first 2 hours after

BOX 4-3 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

From Rozance P, Hay W: Hypoglycemia in newborn infants: features associated with adverse outcomes, Biol Neonate *90:81, 2006.*

birth. 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 hypoglycemia during this normal postnatal period of 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 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 point-of-care method 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 the low blood glucose concentrations.

Because of limitation 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 4-3). The signs and systems of isolated hypoglycemia can be viewed as systemic manifestations of glucopenia (e.g., episodes of cyanosis, apnea, irritability, poor sucking or feeding,) and/or hypothermia accompanied by 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.

MANAGEMENT

The plasma glucose concentration at which intervention is indicated needs to be tailored to the clinical situation and the particular

characteristics of the infant. The AAP clinical report on postnatal glucose homeostasis applies to the first 24 hours after birth. It considers symptoms, mode of feeding, risk factors, and hours of age in a pragmatic approach for these infants. Immediate intravenous glucose treatment might be instituted for an infant with clinical signs and a plasma glucose <40 mg/dL, whereas an at-risk but asymptomatic term formula-fed infant with the same value may only require an increased frequency of feeding and would receive intravenous glucose only if the glucose values decreased to <25 mg/dL (birth to 4 hours of age) or 35 mg/dL (4 to 24 hours of age) (Figure 4-8). Follow-up glucose concentrations and clinical evaluation must be obtained to ensure that postnatal glucose homeostasis is achieved and maintained.

All strategies for the management of neonatal hypoglycemia should be based on the infant's glucose concentration, its trend over time, response to enteral feedings, and clinical signs and symptoms. Because severe, prolonged, symptomatic hypoglycemia may result in neuronal injury, prompt intervention is necessary for infants who manifest clinical signs and symptoms. A reasonable (although arbitrary) cutoff for treating symptomatic infants is 40 mg/dL. This value is higher than the physiologic nadir and higher than concentrations usually associated with clinical signs (Figure 4-8). If the decision is to treat, a plasma sample must be sent to the laboratory just before giving the intravenous minibolus of glucose (200 mg/k of glucose per kg, 2 mL/kg dextrose 10% in water, D10W, intravenously) and/or starting a continuous infusion of glucose (D10W at 80 to 100 mL/k/d). A reasonable goal is to maintain plasma glucose concentration in symptomatic infants between 40 and 50 mg/dL (Figure 4-8).

This algorithm (Figure 4-8) is based on the following observations from Cornblath and Ichord: (1) Almost all infants with proven symptomatic neonatal hypoglycemia during the first hours of life have plasma glucose concentrations lower than 20 to 25 mg/dL; (2) persistent or recurrent neonatal hypoglycemia syndromes present with equally low plasma glucose concentrations; and (3) little or no evidence exists to indicate that asymptomatic neonatal hypoglycemia at any concentration of plasma glucose in the first days of life results in any adverse sequelae in growth or development.

Figure 4-8 is divided into two time periods (birth to 4 hours and 4 to 24 hours) and accounts for the changing values of glucose that occur over the first 24 hours after birth. The recommended values for intervention are intended to provide a margin of safety over concentrations of glucose associated with clinical signs. The intervention recommendations also provide a range of values over which the clinician can decide to refeed or provide intravenous glucose. The target plasma glucose is >45 mg/dL before each feeding. At-risk infants should be fed by 1 hour of age and screened 30 minutes after the feeding. The initial feeding recommendation is consistent with that of the World Health Organization. For infants who are able to tolerate enteral feeds, increasing feeding volume should be the first strategy for actionable thresholds. Milk contains nearly twice the amount of energy as an equivalent volume of 10% dextrose, and breast milk in particular promotes ketogenesis. Gavage feeding may be considered in infants who are not nippling well. Glucose screening should continue for 12 hours of age for infants born to mothers with diabetes and those who are large for gestational age and maintain plasma glucose >40 mg/dL. Late-preterm and infants who are small for gestational age require glucose monitoring for at least 24 hours after birth, because they are more vulnerable to low glucose concentrations, especially if regular feedings or intravenous fluids are not yet established (Figure 4-8).

If inadequate postnatal glucose homeostasis is documented, the clinician must be certain that the infant can maintain normal plasma glucose concentrations on a routine diet for a reasonably extended period (through at least three feed–fast periods) before discharge.

It is recommended that the at-risk asymptomatic infants who have glucose concentrations <25 mg/dL (birth to 4 hours of age) or <35 mg/dL (4 to 24 hours of age) be refed and that the glucose value be rechecked 1 hour after refeeding. Subsequent concentrations, <25 mg/dL, or lower than 35 mg/dL, respectively, after attempts to refeed, necessitate treatment with intravenous glucose (Figure 4-8). Persistent hypoglycemia can be treated with a minibolus (200 mg/k, 2 mL/k D10W) and/or intravenous infusion of D10W at 5 to 8 mL/k per minute, 80 to 100 mL/k/d; the goal is to achieve a plasma glucose concentration >40 to 50 mg/dL (higher concentrations will only stimulate further insulin secretion). Plasma glucose concentration should be checked 30 minutes after the minibolus or glucose infusion, then every 1 to 2 hours until stable and in the normal range. If a subsequent value falls in the treatment range, the bolus can be repeated and the infusion rate increased by 10% to 15%. In some cases, it may require as much as 12 to 15 mg/k/min of intravenous glucose to maintain normoglycemia. In such cases, it may be necessary to place an umbilical venous catheter or peripheral central venous catheter to allow administration of intravenous solution with dextrose concentration greater than 12.5%. If it is not

possible to maintain blood glucose concentration of >45 mg/dL after 24 hours of using this rate of glucose infusion, consideration should be given to the possibility of hyperinsulinemia, which is the most common cause of severe persistent hypoglycemia in the newborn period.

CASE STUDY 5

A 32-year-old gravida 2 is delivered by cesarean section because of failure to progress. Fetal macrosomia was suspected during the pregnancy. Apgars were 6, 7, and 8 at 1, 5, and 10 minutes respectively. The infant's birthweight was 4.6 kg. The infant was breastfed in the delivery room and was screened with a bedside glucose determination 30 minutes after the feeding and the result was 15 mg/dL. A plasma glucose concentration performed at the same time by the laboratory was 18 mg/dL. The infant remained asymptomatic and was breastfed again. One hour later the next bedside screen was 20 mg/dL and the laboratory value was 23 mg/dL.

EXERCISE 5

QUESTIONS

1. What would you do next?
2. What diagnosis are you most concerned about?

ANSWERS

1. The infant should receive intravenous glucose because the level has remained <25 mg/dL despite two feedings.
2. Macrosomia suggests hyperinsulinism.

CASE STUDY 5 (continued)

A minibolus is given and this is followed by an infusion of 5 mg/k/min after the second bedside glucose value of 20 mg/dL. The infant is rescreened with bedside glucose measurements and plasma glucose levels; and despite advancing glucose infusion rate to 16 mg/kg/min, the plasma glucose levels never exceed 40 mg/dL and at 24 hours of age the infant has a seizure. The mother reveals that her previous child had a similar course to this one.

WHEN ARE FURTHER INVESTIGATIONS REQUIRED?

Infants with persistent hypoglycemia or those with inadequate responses to treatment need further evaluation. Recurrent or persistent hypoglycemia (Table 4-2) is defined as conditions that: (1) require infusions of large amounts of glucose (>12 to 16 mg/k/min) to maintain normoglycemia or (2) persist or recur beyond the first 7 to 14 days of life. These infants require specific diagnostic determinations as well as a rapid trial of therapeutic-diagnostic agents to determine cause and therapy. Table 4-2 shows a brief list of these syndromes. Hyperinsulinism, hypopituitarism, and fatty acid oxidation disorders are probably the most common of these rather uncommon causes of neonatal hypoglycemia.

TABLE 4-2 Causes of Recurrent or Persistent Hypoglycemia

Hormone Deficiences	
Multiple endocrine deficiency or congenital hypopituitarism	Anterior pituitary "aplasia" Congenital optic nerve hypoplasia
Primary endocrine deficiency	Isolated growth hormone deficiency Adrenogenital syndrome Adrenal hemorrhage
Hormone excess with hyperinsulinism	Beckwith-Wiedemann syndrome Hereditary defects of pancreatic islet cells
Hereditary deficits in carbohydrate metabolism	Glycogen storage disease Fructose intolerance Galactosemia Glycogen synthase deficiency Fructose, 1-6 diphosphatase deficiency
Hereditary deficits in amino acid metabolism	Maple syrup urine disease Propiionic acidemia Methylmalonic acidemia Tyrosinosis 3-OH-3 methyl glutaryl COA lyse deficiency
Hereditary defects in fatty acid metabolism	Acyl CoA dehydrogenase—medium, long chain Deficiency Mitochondrial β-oxidation and degradation defects

From Cornblath M, Ichord R: Hypoglycemia in the neonate, Semin Perinatol *24:145, 2000.*

An underlying metabolic or hormonal etiology should be suspected when the hypoglycemia is of unusual severity or occurs in an otherwise low-risk infant. Some clues to a possible underlying metabolic-hormonal disorder include:

- Symptomatic hypoglycemia in a healthy, well grown term infant
- Hypoglycemia with seizures or abnormalities of consciousness
- Persistent or recurrent hypoglycemia

- Hypoglycemia in association with other abnormalities (midline defects, micropenis, exophthalmos, labile thermoregulation)
- Hypoglycemia requiring >10 mg/kg/min of glucose
- Family history of sudden infant deaths or developmental delay

CONCLUSION

Current evidence does not support a specific concentration of glucose that can discriminate euglycemia from hypoglycemia or can predict the acute or chronic irreversible neurologic damage that will result. Once observed, a significantly low concentration of glucose in the plasma of an at-risk asymptomatic infant should be confirmed and treated to restore glucose values to a normal physiologic range. Recognizing infants at risk of disturbances in postnatal glucose homeostasis and providing a margin of safety by early measures to prevent (feeding) and treat (feeding and intravenous glucose infusion) are the goals of management.

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