

Neonatal Hyperglycemia

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OBJECTIVES

After completing this article, readers should be able to:

1. Explain the relationship of the frequency of hyperglycemia with the birthweight and gestational age of the neonate.
2. List factors that may decrease glucose tolerance in the neonate.
3. Describe the major mechanism(s) contributing to altered regulation of neonatal glucose metabolism.
4. List the untoward effects of hyperglycemia in the neonate.
5. Describe the beneficial effects of insulin infusion in selected neonates.

Case Study

A preterm male infant was born at 26 weeks' gestation weighing 900 g, with a birthweight percentile below the 3rd percentile and a head circumference at about the 25th percentile. His Apgar scores were 4 and 5 at 1 and 5 minutes, respectively, and he required intubation and ventilation in the delivery room. The infant was given artificial surfactant and maintained on a respirator with "moderate to high settings." Several saline boluses were administered for hypotension, and dopamine was started to maintain a mean arterial blood pressure above 30 mm Hg. Initial serum glucose concentrations were in the range of 1.67 to 2.76 mmol/L (30 to 50 mg/dL). The infant was given 10% dextrose at a rate of 100 mL/kg per day.

By the second day of life, the serum glucose concentration was in the range of 5.55 to 8.33 mmol/L (100 to 150 mg/dL), and the dextrose infusion, which now contained sodium chloride and potassium acetate, was increased to 150 mL/kg per day because of polyuria of 6 mL/kg per hour. The infant remained NPO. Subsequent glucose concentrations over the next 24 hours increased to more than 13.88 mmol/L (250 mg/dL), and glycosuria was noted. At this time,

the intravenous (IV) fluid rate was 225 mL/kg per day ("to maintain hydration") and the glucose infusion rate was 16 mg/kg per minute. The IV solution was changed to 5% dextrose, but the glucose concentration remained high, increasing to 17.76 mmol/L (320 mg/dL), then 22.65 mmol/L (410 mg/dL). Insulin treatment was started at 0.05 U/kg per hour, along with an IV infusion of 1 g/kg per day of amino acids.

By the fourth day of life, the infant continued to receive IV insulin and was tolerating total parenteral nutrition (TPN) with 5% dextrose providing 12 mg/kg per minute and 2 g/kg per day of amino acids via a central venous catheter. Glucose concentrations remained in the range of 5.55 to 8.33 mmol/L (100 to 150 mg/dL). One episode of hypoglycemia (glucose, <0.56 mmol/L [<10 mg/dL]) with an apparent seizure was noted after the infant was switched to a peripheral catheter for the TPN solution and it infiltrated, probably for 2 hours before being discovered.

Enteral feeding was started on the 10th day of life. Other than the development of chronic lung disease, one episode of suspected necrotizing enterocolitis without pneumatosis intestinalis, and one episode of *Staphylococcus epidermidis* sepsis, the infant's course was relatively uncomplicated. At term gestation, his weight remained much less than the 3rd percentile, growth had shown no catch-up, and he was not yet approaching a standard growth curve for infants of 26 weeks' gestation. Subsequent development was markedly delayed.

Questions to consider (feel free to send in your answers to these questions and any questions of your own for the "experts" to consider and discuss about this case)

1. Why did this infant develop hyperglycemia?
2. What role did the infant's intrauterine growth restriction play in the pathogenesis of hyperglycemia?
3. Did the clinicians decrease the IV glucose infusion rate sufficiently to correct the hyperglycemia?
4. Did the IV amino acids play a role in treating the hyperglycemia?
5. Should the clinicians have used insulin?
6. Why did the infant develop hypoglycemia and possibly a hypoglycemic seizure when the IV line infiltrated?
7. Was the delayed development in this infant directly related to the hyperglycemia?

William W. Hay, Jr, MD
Coeditor

Introduction

Hyperglycemia has become a significant risk factor for morbidity and mortality as smaller and more fragile infants survive during the neonatal period. Historically, hyperglycemia has been attributed to excessive IV glucose infusion. More recent studies indicate that physiologic and biochemical mechanisms, leading to

ABBREVIATIONS

AGA:	appropriate for gestational age
ELBW:	extremely low birthweight
GLUT:	glucose transporter
LBW:	low birthweight
PNDM:	permanent neonatal diabetes mellitus
RQ:	respiratory quotient
SGA:	small for gestational age
TNDM:	transient neonatal diabetes mellitus
TPN:	total parenteral nutrition
VLBW:	very low birthweight
YSI:	Yellow Springs Instrument Company glucose analyzer

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excess glucose production, insulin resistance, or glucose intolerance, underlie the development of hyperglycemia in preterm infants and sometimes inhibit efforts to maintain normal glycemia in the neonate. The sequelae of these disturbances in glucose metabolism are extensive.

Diagnosis

Hyperglycemia generally is defined as a whole blood glucose concentration greater than 6.66 to 6.94 mmol/L (>120 to 125 mg/dL) or a plasma glucose concentration greater than 8.05 to 8.33 mmol/L (>145 to 150 mg/dL), regardless of the neonate’s gestational age, weight, or postnatal age. Although affected neonates often are “asymptomatic” or have signs indicative of other disease processes, recognizable signs specific to hyperglycemia may include dehydration due to an osmotic diuresis, weight loss, failure to thrive, fever, glycosuria, ketosis, and metabolic acidosis. The latter three signs are particularly common among infants who have transient or permanent neonatal diabetes mellitus.

Because such clinical signs are unreliable indicators of the presence or degree of hyperglycemia, it is necessary to measure glucose concentration by glucose analyzers. Considerable controversy surrounds the use of different instruments that have highly variable degrees of accuracy and reliability. The spectrophotometric glucose oxidase method is the gold standard, but using a central hospital laboratory to analyze the repeated blood samples necessary to manage the sick neonate, often moment to moment, may be impractical. One alternative may be the use in the nursery of the Yellow Springs Instrument Company glucose analyzer (YSI), which has excellent correlation ($r=0.99$) with the manual, laboratory-performed spectrophotometric glucose oxidase method. In contrast, glucose reagent strips and glucose reflectance meters, whether read visually or using a built-in algorithm, have much weaker correlations with the laboratory glucose oxidase method ($r=0.70$ to 0.83).

Several studies have compared

the YSI with glucose reflectance meters among randomly selected infants. The reflectance meters have correlations with the YSI ranging from $r=0.88$ to 0.96 for cord blood and from $r=0.64$ to 0.86 for capillary blood (Table 1), demonstrating a fundamental shortcoming of handheld glucose reflectance meters to determine blood glucose concentration in the neonate. More recently, improved glucose reflectance meters have become available. As with all reflectance meters, however, consistently careful and accurate use is necessary to achieve optimal performance.

Several noninvasive techniques for measuring glucose concentration have been proposed and evaluated. The first used near-infrared spectroscopy, usually on a finger, the inner lip, or oral mucosa. However, this method is not very accurate. Cross-validated standard errors of prediction have ranged from 2.16 to 3.05 mmol/L (39 to 55 mg/dL) in normoglycemic adults. More traditional ultraviolet and infrared spectroscopy are impractical because of limited depth of penetration and the interfering absorption of these wavelengths of light by many photoreactive substances. Another form of noninvasive glucose measurement involves direct analysis of body fluids other than blood (eg, saliva, sweat, urine, or tears). Unfortunately, the correlation between blood glucose concentration and glucose concentration in excreted fluids is

weak. In addition, the time lag between glucose entering the bloodstream and its excretion into body fluids is not well documented in the neonate. Thus, analysis of body fluids other than blood is inappropriate for the diagnosis and management of hyperglycemia in the neonate.

Epidemiology

The incidence of hyperglycemia varies widely, but nearly all studies show that low birthweight (LBW) is the primary significant risk factor at any gestational age; preterm birth ranks a close second. Thus, the incidence of hyperglycemia is related inversely to birthweight in the preterm infant, ranging from about 2% in infants who weigh more than 2,000 g to 45% in those who weigh less than 1,000 g and up to 80% in extremely low-birthweight (ELBW) infants weighing less than 750 g.

Many other factors also are associated with hyperglycemia. In most studies there is a significant relationship between blood glucose concentration and the initial rates of IV glucose administration (Fig. 1). Over longer periods of observation, however, the correlation between blood glucose concentration and the rate of glucose infusion decreases, as clinicians attempt to treat the hyperglycemia by decreasing the rate of glucose infusion. In fact, glucose administration rates as low as 3 to 4 mg/kg per minute have been associated with persistent hyperglycemia.

TABLE 1. Accuracy of Reflectance Meters Versus the Yellow Springs Instruments Co. Glucose Analyzer

DIFFERENCE BETWEEN MEANS (%)	CORD BLOOD	HEEL STICK BLOOD	P VALUE
Reflectance meter			
Glucometer M	-9.3	-23.2	
Diascan S	0.4	-0.4	
Accu-Chek II	1.2	16.4	
One Touch	35.2	25.6	
Correlation coefficient			
Glucometer M	0.88	0.64	<0.05
Diascan S	0.96	0.71	<0.01
Accu-Chek II	0.91	0.71	<0.05
One Touch	0.92	0.86	NS

From Lin HC, Maguire C, Oh W, Cowett R. Accuracy and reliability of glucose reflectance meters in the high risk neonate. J Pediatr. 1989;115:998-1000.

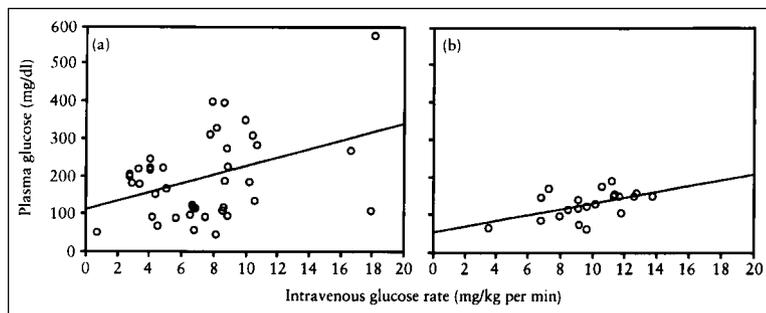


FIGURE 1. The plasma glucose concentration relative to the rate of IV glucose administered in a representative neonate in the 500-g birthweight category (a) and in one in the 900-g birthweight category (b). From Cowett AA, Farrag HM, Gelardi NL, Cowett RM. *Hyperglycemia in the micropremie: evaluation of the metabolic disequilibrium during the neonatal period.* *Prenat Neonatal Med.* 1997;2:360–365.

Positive relationships also have been found between hyperglycemia and the severity of clinical problems in the neonate, as estimated by the Apgar score, the fractional concentration of inspired oxygen, and the respiratory distress score. A negative correlation also exists between blood glucose concentration and blood hematocrit, serum bilirubin concentration, and plasma total protein concentration.

Etiology

GLUCOSE INFUSION

Exogenous glucose infusion has a major impact on the development of hyperglycemia. Among preterm

infants receiving continuous glucose infusions at 8 mg/kg per minute, 11 mg/kg per minute, or 14 mg/kg per minute, practically none of the infants in the lowest glucose infusion group developed hyperglycemia. In contrast, 50% or more of the infants in the middle infusion group and all of the infants in the highest infusion group developed increased blood glucose concentrations (Fig. 2).

LIPIDS

It is important to point out, however, that critically ill neonates who are receiving even lower rates of glucose infusion also have developed hyperglycemia, which has led to speculation about alternative etiologies.

For example, the lipid component of parenteral nutrition may contribute to the glycemic response apart from that of the exogenous glucose (dextrose) component. Several studies have shown a dose-response relationship between the plasma concentration of lipid and blood glucose. In preterm infants receiving either 0.25 or 0.5 g/kg per hour of Intralipid® lipid emulsion, a

steady and sustained increase in serum glucose concentrations develops during the infusion and up to 1 hour postinfusion. These exceedingly high lipid infusion rates are not used in preterm or term infants, but the results demonstrate that lipids and lipid components, especially free fatty acids, can promote hyperglycemia. Increased plasma free fatty acid concentrations decrease peripheral glucose utilization, primarily by substituting carbon and altering enzymatic activity that preferentially leads to fatty acid carbon oxidation rather than glucose oxidation. Fatty acids also inhibit the effect of insulin to suppress hepatic glucose production. These two conditions—peripheral glucose intolerance and central (hepatic) insulin resistance—increase glucose concentrations in the plasma. As a result, insulin concentrations often are paradoxically greater after lipid infusion. This seemingly contradictory trend in glucose and insulin concentrations may be explained by the direct effect of fatty acids on promoting insulin secretion as well as the inhibition of insulin action in the periphery.

STRESS

Stress, as measured by increased plasma cortisol concentrations, also appears to be an important risk factor for the development of hyperglycemia. Sick neonates frequently suffer physiologic stress from both their disease processes and the medical interventions provided (eg, painful procedures such as venipuncture and cutdowns, endotracheal tube irritation during ventilator treatment, catecholamine infusions). However, the relationship between cortisol as an indicator of stress and the development of hyperglycemia can be confusing because the cortisol response may be suppressed by hyperglycemia in a negative feedback relationship. Neonates also can develop marked hyperglycemia during and after surgical procedures. Postsurgical hyperglycemia appears to be due to increased cortisol secretion during surgery; hyperglycemia noted immediately after the start of anesthesia appears to be due to cate-

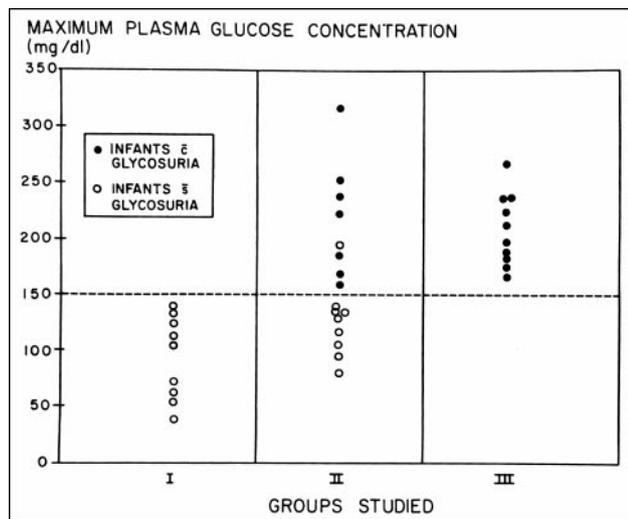


FIGURE 2. Incidence of glycosuria among three groups of infants categorized according to maximal plasma glucose concentration obtained during steady state. From Cowett RM, Oh W, Pollak A, Schwartz R, Stonestreet BS. *Glucose disposal of low birthweight infants: steady state hyperglycemia produced by constant intravenous glucose infusion.* *Pediatrics.* 1979;63:389–396.

choline release in response to induction.

In support of these factors causing or amplifying hyperglycemia after surgery or stressful invasive procedures, fentanyl treatment during and after surgery has decreased the incidence of hyperglycemia and increased circulating concentrations of epinephrine, glucocorticoids, and glucagon as well as the insulin:glucagon ratio. Epinephrine decreases insulin secretion from the pancreatic beta cell and interferes with peripheral insulin action. Glucagon promotes glycogenolysis and release of hepatic glucose. Glucocorticoids promote gluconeogenesis by increasing protein breakdown and, thus, the supply of amino acids. Glucocorticoids also enhance hepatic enzyme activity in the gluconeogenic pathway, particularly phosphoenolpyruvate carboxykinase, which is the rate-limiting enzyme for gluconeogenesis, and glucose-6-phosphatase, which releases glucose into the circulation.

INSULIN RESISTANCE

The theory of insulin resistance in peripheral tissues, especially skeletal muscle, causing hyperglycemia has been tested repeatedly. In general, LBW infants given a glucose challenge (eg, 1 g/kg IV bolus) have shown variable increases in plasma insulin concentration. Among preterm small for gestational age (SGA) and preterm appropriate for gestational age (AGA) infants who have relatively normal insulin secretion, however, plasma free fatty acid and beta-hydroxybutyrate concentrations still increase significantly. These observations indicate that fat mobilization, with release of fatty acids and their subsequent beta oxidation in the liver, is not suppressed by glucose-stimulated insulin secretion. Such findings are consistent with a decreased sensitivity to insulin among LBW infants, particularly those who are sufficiently mature to have adipose tissue stores, even if SGA, and the enzymatic capacity to mobilize fatty acids from adipose tissue. This subject remains controversial. Animal data indicate normal or even increased insulin action in early gestation in relation to glucose

utilization, despite lower concentrations of insulin receptors on hepatocytes. Furthermore, IV infusions of insulin in infants who have hyperglycemia usually produce prompt and rapid decreases in plasma glucose concentration.

INSULIN-DEPENDENT DIABETES MELLITUS

An unusual, but important, etiology of hyperglycemia in the infant is insulin-dependent diabetes mellitus. Transient neonatal diabetes mellitus (TNDM) presents early in postnatal life; 75% of cases present in the first 10 days of life with weight loss, polyuria, dehydration, glycosuria, and hyperglycemia. Concentrations of C-peptide and plasma insulin are low. TNDM usually does not resolve for several weeks to months. A rebound in C-peptide concentration typically marks the resolution. When TNDM does not resolve, which is much rarer, it is known as permanent neonatal diabetes mellitus (PNDM). Both conditions are caused by endogenous insulin deficiency due to failure of pancreatic beta cells. The pathogenesis is unknown; anti-islet antibodies and typical human lymphocyte antigen types have not been reported in infants who have either TNDM or PNDM.

A family history of diabetes is found in about one third of cases of TNDM, with the condition occurring more frequently among siblings and even in mother and offspring. There has been no evidence of common loci associated with diabetes mellitus in such families nor have tissue antibodies associated with autoimmune causes of diabetes been detected. Detailed evaluations of isolated cases of familial PNDM have shown the infants to have normal secretion of glucagon, cortisol, and growth hormone. Insulin secretion has not been assessed, but C-peptide concentrations are low. Results of insulin-binding studies in fibroblasts, erythrocytes, and B lymphocytes appear normal and do not suggest end-organ insulin receptor insensitivity. Such cases of PNDM may be the result of genetic inheritance (a dominant trait with variable penetrance) and may represent a unique form of diabetes mellitus.

OTHER

Other causes of hyperglycemia include the use of medications such as theophylline and dexamethasone. Individual cases reported in the literature associate hyperglycemia with prostaglandin E₁ and chromosome deletion (46,xxDq- on number 13). Sepsis also has been implicated.

Pathophysiology

As described previously, glucose homeostasis becomes more disordered with decreasing maturity of the neonate. In human fetuses, insulin is produced in the pancreas as early as the 11th week of gestation. However, this insulin is not released readily in response to hyperglycemia even as late as the 20th week of gestation. Unresponsiveness to insulin action may continue even later in gestation. Studies using the euglycemic hyperinsulinemic clamp technique in neonates born at 31 to 34 weeks' gestational age have shown persistent glucose production during steady-state insulin infusions. This endogenous glucose production occurs at even very high rates of insulin infusion that range from 0.2 up to 4.0 mU/kg per min (Fig. 3). Although a postinsulin receptor defect may be responsible, such as glucose transporter or enzyme regulation in the glycolytic, glycogenolytic, or gluconeogenic pathways, there is no specific evidence for these possible mechanisms. Others have suggested that such delays in insulin sensitivity leading to hyperglycemia are the result of obscure or poorly manifested cases of stress and counterregulatory hormonal action. Clearly there is considerable need for definitive studies of such possible mechanisms responsible for insulin sensitivity in these preterm infants as well as in developing fetuses and otherwise normal preterm infants.

Excessive or inappropriate (for insulin secretion rates and plasma insulin concentrations) glucose production also can promote or prolong hyperglycemia. Very low-birthweight (VLBW) and ELBW infants can develop surprisingly high rates of glucose production, both from glycogenolysis and from glu-

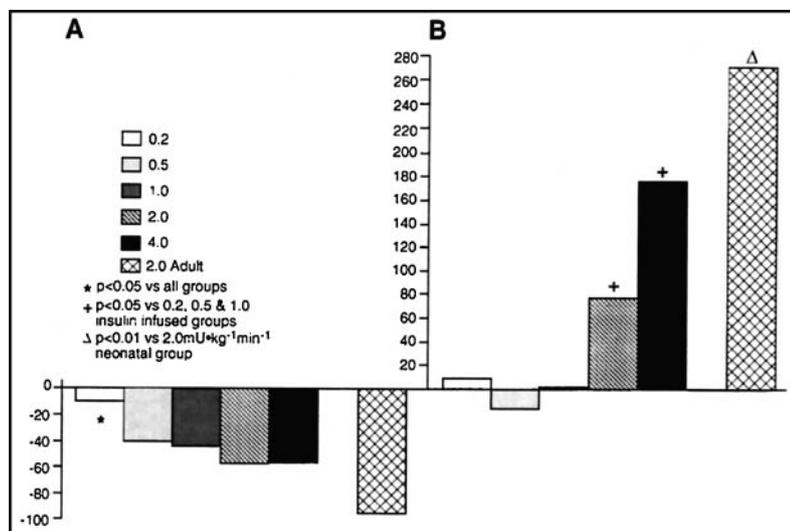


FIGURE 3. Percent decrease in endogenous glucose production (A) and percent increase in glucose utilization (B) subdivided by various insulin infusion rates administered to neonates and 2 mU/kg per minute administered to adults. From Farrag HM, Nawrath LM, Healy JE, et al. Persistent glucose production and greater peripheral sensitivity to insulin in the neonate versus the adult. *Am J Physiol.* 1997;272:E86–E93.

coneogenesis, relatively soon after preterm birth. Studies of endogenous glucose production in ELBW neonates during steady-state infusion of stable isotope tracers of glucose have documented hepatic glucose production rates as great as 0.05 mg/g (liver weight) per minute, which is comparable to values reported in fasting adults. Correlation between glucose production rates and plasma insulin concentrations is seldom significant, perhaps because only relatively narrow ranges of both plasma glucose and insulin concentrations have been studied. Interestingly, glycerol is a principal source of gluconeogenesis when early gluconeogenesis in preterm infants is active. This observation is consistent with previous studies that have shown only limited conversion of alanine (and other amino acids) to glucose in preterm infants, indicating that amino acid conversion to glucose is a developmental process that occurs later.

Glucose Homeostasis and Glucose Transporters

Glucose is transported across the plasma membrane of cells by a family of structurally similar proteins called glucose transporters (GLUTs). The GLUTs are expressed in a tissue-specific manner (Table 2).

Hyperglycemia may be more common in very preterm infants due to inadequate development of the insulin-dependent GLUT-4-mediated glucose transport system. GLUT-4 develops progressively during gestation, coincident with the growth of insulin-sensitive tissues, primarily skeletal muscle, as well as the production of insulin and the concentration of insulin in the plasma. Fetal hyperglycemia has been shown to decrease GLUT-4 expression, which would tend to produce insulin resistance, and to decrease skeletal muscle GLUT-1, which would tend to produce glucose intolerance. Hypoglycemia either has no effect or increases GLUT-1 and GLUT-4. Studies among different species, different tissues, and different durations of glycemic change demonstrate considerable variation in GLUT expression and relation to glucose metabolism. Thus, study of GLUTs, the regulation of their expression and activity, and their effect on glucose metabolism, particularly with conditions such as hyperglycemia, are important and should be helpful in understanding molecular aspects of pathologic glycemic conditions in neonates.

GLUT-1 and GLUT-3 are constitutive transporters responsible for basal glucose uptake in many tissues. They are characterized by a

high affinity for glucose compared with other GLUTs, meaning that GLUT-1 and GLUT-3 can be effective even at low glucose concentrations. This characteristic is particularly important in the central nervous system (CNS), where GLUT-1 and GLUT-3 are the primary transporters for glial and neuronal cells, respectively. Gene expressions of GLUT-2 and GLUT-3 are determined by the metabolic needs of the CNS. Because these transporters are not sensitive to insulin, CNS glucose uptake is not affected by plasma insulin concentrations. The glucose transport capacity of the combined brain vascular endothelial cell GLUT-1 and neuronal GLUT-3 expression appears to be great enough to allow sufficient glucose uptake for most of the brain's glucose needs, even in the presence of modest hypoglycemia.

GLUT-2 occurs only in hepatocytes and pancreatic beta cells; its expression and effect on glucose uptake are regulated developmentally and by plasma glucose and insulin concentrations. GLUT-2 is a low-affinity transporter, allowing glycogenolysis and gluconeogenesis to release glucose into the plasma in response to small reductions in glucose concentration, even in the normal glucose concentration range, which helps to prevent hypoglycemia. Similarly, the low affinity of GLUT-2, in concert with glucokinase function, allows pancreatic beta cells to recognize modest increases in plasma glucose concentration, leading to increased insulin secretion, which helps prevent hyperglycemia. Although the beta cells of preterm infants respond to hyperglycemia by increasing insulin secretion, this process is diminished, in part due to decreased expression or function of the immature glucose sensor (GLUT-2 plus glucokinase) and in part due to decreased activity of other metabolic linkages in beta cells. The resulting increase in plasma insulin concentration often is not adequate to prevent hyperglycemia.

Hyperglycemia also may be due to hepatic and peripheral insulin resistance that results in diminished effectiveness of insulin in inhibiting

TABLE 2. Glucose Transporters

GLUCOSE TRANSPORTER	PRIMARY TISSUE	CHARACTERISTIC FUNCTION	RELATIVE AFFINITY FOR GLUCOSE
GLUT-1	All tissue; particularly important in central nervous system (CNS) (glial cells) and testes	Basal glucose uptake	+++
GLUT-2	Liver and pancreas	Hepatic glucose uptake and release Component of B-cell glucose sensor together with glucokinase	+
GLUT-3	Most tissues; particularly important in CNS (neurons)	Basal glucose uptake	++++
GLUT-4	Muscle and fat	Insulin-sensitive transporter	++
GLUT-5	Intestine and liver	Fructose uptake	+
GLUT-6	(pseudogene)		
GLUT-7	Liver	Microsomal transporter	?

Adapted from Lane R, Simmons R. Semin Neonatal Nutrit Metab. 1997;4:4.

hepatic glucose production and promoting peripheral glucose utilization. LBW infants often require exogenous insulin to resolve hyperglycemia despite an almost twofold rise in endogenous plasma insulin concentration. In most preterm infants, endogenous glucose production cannot be inhibited completely (no more than 50% to 60%) by any level of insulinemia, and only very high concentrations of insulin (more than 10-fold above normal) enhance peripheral glucose utilization. Post-insulin receptor defects are considered most likely to be responsible. Studies of multiple species in the early newborn period demonstrate that hepatocytes express a relatively high amount of GLUT-1 but relatively low levels of GLUT-2. The decreased GLUT-2 expression may limit hepatocyte sensitivity and responsiveness to an increase in insulin concentration that accompanies hyperglycemia, resulting in an inability to decrease hepatic glucose production.

GLUT-4 is found in insulin-sensitive tissues, primarily skeletal muscle, heart, and adipose tissue. When translocated by insulin to the cell membrane, GLUT-4 helps to decrease glucose concentration by

enhancing cellular glucose uptake. In the newborn rat, GLUT-4 does not reach adult levels until day 14 or 15. Decreased skeletal muscle expression of GLUT-4 also may contribute to the insulin resistance and hyperglycemia seen in ELBW/LBW infants. Similarly, decreased cardiac expression of GLUT-4 has been seen in experimental conditions in the fetus in response to chronic hyperglycemia, perhaps providing a mechanism to limit excessive glucose uptake.

Enzyme regulation also is an important component for establishing neonatal glucose homeostasis. Preterm neonates may have immature biochemical pathways that metabolize glucose incompletely. The fetal liver produces noninsulin-dependent hexokinase in preference to glucokinase. In response to insulin, only a small amount of glucokinase is available for glucose transport. The enzymes necessary for converting glucose to glycogen, which increase in activity with increasing gestational age, may be deficient in the immature neonate. These enzymes include phosphoglucomutase, uridine diphosphoglucose (UDPG) pyrophosphorylase, and UDPG glycogen synthetase.

Complications

Neonatal hyperglycemia has been associated with a wide spectrum of sequelae, ranging from the clinically manageable (dehydration) to the devastating (death). Although rare today, previous reports of intracranial hemorrhage and death among preterm infants who were markedly hyperglycemic and other reports documenting abnormal neurodevelopmental outcome in such infants indicated a much worse severity of illness and much more ominous prognosis than occurs today. For example, among selected groups of preterm infants ranging from 24 to 34 weeks' gestational age who had severe and protracted hyperglycemia in earlier reports, more than 50% subsequently died. The predominant cause of death was intracranial hemorrhage. Hyperglycemia causes a rise in serum osmolarity; each increment of 1 mmol/L (18 mg/dL) in blood glucose concentration accounts for a rise of 1 mOsm/L in serum osmolarity. If serum osmolarity exceeds 300 mOsm/L (roughly, a serum glucose value of 22.2 mmol/L [400 mg/dL]), rapidly shifting water may cause cerebral hemorrhage. Cellular damage from such an insult apparently is augmented by pre-existing hyperglycemia. Observa-

tions in neonatal rats have shown that moderate hyperglycemia significantly increases morphologic damage throughout the forebrain with induced ischemic events. The pathophysiology of increased ischemic damage during hyperglycemia is unclear; hypotheses include hyperosmolarity, excessive lactic acidosis, and decreased regional cerebral blood flow.

Hyperosmolarity also can lead to a potential osmotic diuresis that results in polyuria and dehydration. The increase in serum osmolarity associated with hyperglycemia theoretically puts the tiny infant at risk for osmotic diuresis and dehydration. Most short-term studies have failed to observe such an effect in LBW infants who have hyperglycemia; hyperglycemic periods of greater than 5 hours may be necessary to detect a diuretic effect.

Another potential effect of aggressive glucose administration is steatosis and associated impairment in secretion of hepatic triglycerides. Although steatosis rarely causes clinical signs in the neonate, it can be detected by modest elevations of liver transaminases.

Hyperglycemia also might jeopardize respiratory function by raising the respiratory quotient (RQ), the ratio between CO₂ generated and O₂ consumed. Carbohydrate oxidation results in an RQ of 1.0. Because lipogenesis produces CO₂ without consuming CO₂, the resulting increase in CO₂ production requires an increase in minute ventilation that may compromise the fragile ELBW/LBW infant. Studies in infants have demonstrated this increase in CO₂ production, but the clinical significance remains unclear.

Another complication of hyperglycemia is electrolyte imbalance. A significant finding in neonates who have glycosuria is an increase in sodium excretion due to increased filtered sodium load, even with minimal glycosuria. Creatinine clearance is altered significantly during the infusion. Hyperglycemia theoretically can trigger partial suppression of endogenous glucose production, which is accompanied in adults by suppression of whole-body proteolysis. In neonates, however, this does not appear to be the case. Hertz et al

studied five clinically stable neonates of less than 28 weeks' gestation. Each received glucose infusions of 6 mg/kg per minute, followed by infusions of 9 mg/kg per minute, during which time the investigators traced the appearance of leucine and phenylalanine in the blood as markers of proteolysis. They reported that proteolysis was not suppressed during glucose infusion, even with near-complete suppression of glucose production. It is unclear if the continuation of proteolysis in the infant who has hyperglycemia is a benefit or a detriment; high rates of proteolysis and protein turnover may be part of the normal growth process, which is desirable, particularly in the LBW neonate. Suppression of proteolysis does not appear to be associated with hyperglycemia, but further studies are required to evaluate the implications of these data.

Treatment

The treatment of neonatal hyperglycemia must be based on the diagnosis and suspected etiology of the condition in each case. Hyperglycemia detected by reagent strips read visually should be confirmed by laboratory methods. The exogenous glucose infusion rate and medications being administered should be noted. Urine output, urine glucose concentration, and plasma glucose concentration should be measured to assess the potential for dehydration and osmotic diuresis. Serum electrolytes should be determined to calculate fluid replacement therapy. Weight should be measured to determine hydration status.

When the blood glucose concentration is in the range of 6.9 to 19.43 mmol/L (125 to 350 mg/dL), reducing exogenous glucose administration should be sufficient to ameliorate the hyperglycemia. The rate of infusion should be decreased gradually, by 1 to 2 mg/kg per minute every 2 to 4 hours, with frequent monitoring of plasma or blood glucose concentrations until normoglycemia is achieved or until the glucose infusion rate reaches 3 to 4 mg/dL and hyperglycemia remains severe (>19.43 mmol/L [>350 mg/dL]). It is important to remember

that 40 to 60 kcal/kg per day is necessary to spare protein for subsequent somatic growth.

It is appropriate to feed infants who have hyperglycemia unless other clinical problems are considered severe enough to prevent feeding. Early introduction of IV amino acids by parenteral infusion has been associated with decreased incidence and severity of hyperglycemia and hyperkalemia. There is considerable theoretical rationale for this approach; certain amino acids, such as leucine, valine, isoleucine, glutamine, and arginine, are known insulin secretagogues. Furthermore, such amino acids probably are necessary for the normal growth and development of the pancreas and the pancreatic islet and beta cells. At least glutamine and perhaps leucine also may promote insulin action and the disposal of glucose in skeletal muscle.

Enteral feeding has been shown to promote pancreatic function and the secretion of insulin. Even minimal amounts, such as in "minimal enteral feeding" regimens, induces the gut production of "enteroinsular hormones," also known as "incretins," including gastric inhibitory polypeptide and pancreatic polypeptide. These hormones increase insulin secretion by direct actions on the pancreatic beta cells. Such observations warrant efforts to feed preterm infants who have hyperglycemia, even if full enteral feedings cannot or should not be attempted.

If severe hyperglycemia persists, exogenous insulin administration may be warranted. Guidelines about when to use insulin treatment and how to provide this form of therapy remain highly controversial and vary widely among clinicians and institutions. Many consider insulin treatment unnecessary, others use it sparingly if at all, and many use it according to fairly liberal guidelines, considering that it also might provide a positive protein balance, improve nutrition, and control glucose concentration. Reasonable guidelines indicate that insulin treatment should be reserved until plasma glucose concentrations exceed 16.7 to 22.2 mmol/L (300 to 400 mg/dL) despite reducing the

glucose infusion rate to less than 3 to 4 mg/kg per minute.

The usual method of insulin administration involves a continuous infusion, beginning at 0.02 to 0.05 U/kg per hour. Although higher infusion rates have been used, they usually are not necessary and increase the risks of hypokalemia and subsequent hypoglycemia. Hypokalemia can be prevented by the addition of potassium to IV solutions during the infusion. Normal infusion rates of potassium usually are sufficient, but during insulin treatment, frequent monitoring of serum potassium concentrations is warranted. Small IV boluses of potassium (0.1 mEq potassium as potassium chloride or potassium acetate) can be added every 1 to 2 hours if hypokalemia is significant and persistent. Urine flow rates should be good before repeating potassium doses.

Hypoglycemia is a potentially severe problem if insulin is administered through a single IV line. If it becomes disconnected, the infused insulin lasts much longer in the circulation than the infused glucose or endogenously produced glucose, leading to potentially severe hypoglycemia. Although this has been an infrequent complication of insulin treatment, it remains a serious potential risk. Obviously, blood glucose concentration should be measured repetitively and frequently (every 1 to 2 hours or whenever signs of possible hypoglycemia develop) during the administration of insulin to the neonate.

VLBW infants younger than 30 weeks' gestational age can increase glucose tolerance using insulin infusion therapy. After one treatment of 3 to 6 hours in duration, such infants have been shown to increase glucose tolerance by 50% to 300% and were able to maintain normoglycemia thereafter. ELBW very preterm infants may not demonstrate such dramatic improvement in glucose tolerance, although reports have noted that observations were made on much sicker infants who probably had much higher concentrations of counterregulatory hormones. Other factors may contribute to persistent glucose intolerance, including insulin resistance. A few

infants who initially responded to insulin therapy have developed resistance to insulin within hours to days. Despite increasing insulin infusion rates to as high as 16 U/kg per hour, resistance persisted. None of these neonates was septic, but all were receiving antibiotic therapy for other conditions as well as ventilator support.

One major caveat regarding continuous insulin infusion is the variable delivery of insulin due to its adsorption to the walls of plastic tubing in the IV pump. An infant may require initially increased rates of insulin infusion to overcome this loss. This increased rate can lead to hypoglycemia as the infusion continues and the rate of adsorption slows markedly. One approach to prevent or limit this problem is to flush the insulin delivery system with diluted insulin 2 hours before beginning therapy. Others have mixed the insulin infusion with albumin at a concentration of 0.3 g/100 mL of solution to decrease adsorption.

Conclusion

Hyperglycemia is a frequent complication in the often small and growth-restricted preterm infant that can be a formidable problem to treat. When the neonate also is critically ill, vulnerability to the complications of hyperglycemia multiplies. Hyperglycemia may be a primary cause of pathology or a marker of severe stress. Efforts to prevent hyperglycemia should include general measures to improve the health of the infant and attempts to treat pathophysiologic conditions and diseases. Feeding early, both parenterally and enterally, helps improve insulin production and insulin sensitivity as well as general metabolism. When hyperglycemia is severe and prolonged, insulin in carefully titrated IV infusions has been successful in decreasing the circulating plasma glucose concentration. This approach should not be used in isolation, however, without first trying measures to promote endogenous insulin production and action to treat other illnesses and to decrease IV glucose infusion from abnormally high rates above 12 to 14 mg/kg per minute.

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Pediatrics in Review 1999;20:e16

DOI: 10.1542/pir.20-7-e16

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