NEONATAL HYPOGLYCAEMIA- - Dr. Leya Sara Samuel

- Hypoglycemia is the most common metabolic disturbance occurring in the neonatal period.
- Screening at-risk infants and the management of low blood glucose levels in the first hours to days of life is a frequent issue in the care of the newborn infant.
- Yet, a clear definition of neonatal hypoglycemia is lacking.
- Current screening guidelines and management algorithms are based on limited evidence, relying more on expert opinion to guide recommendations.
- Despite a better understanding of early glucose homeostasis and transitional hypoglycemia in the first 48 hours of life, gaps in our knowledge persist.
- Observations have shown that healthy infants experience transient hypoglycemia as a part of the normal adaption to extrauterine life, with a decline in blood glucose concentrations to values as low as 20 to 25 mg/dL in the first two hours of life.
- However, because we do not routinely measure blood glucose concentrations in healthy infants without risk factors for hypoglycemia, it is difficult to define 'normal' levels of blood glucose in the first 48 hours of life.
- As Harding et al. question: "even if healthy infants experience low glucose concentrations, can we extend these values to infants at risk of impaired metabolic adaption?"
- And how low is too low?
- A 1988 multicenter nutritional study by Lucas et al. suggested a blood glucose concentration <47 mg/dL as the critical threshold associated with adverse neurodevelopmental outcomes.
- The study looked at blood glucose levels in 661 preterm infants with a birth weight of <1850 grams enrolled in a nutritional study investigating early feeding strategies and cognitive outcomes.
- Investigators found that the number of days of blood glucose concentrations <47 mg/dL associated with lower motor and mental developmental scores on the Bayley Scales of Infant Development at 18 months corrected age.
- Infants that experienced hypoglycemia (glucose <47 mg/dL) on 5 or greater days had 3 to 5 times increased risk of neurodevelopmental impairment.
- The authors concluded that "even moderate hypoglycemia is associated with a considerable increase in adverse neurodevelopmental sequelae" and called for a reevaluation of the then current practice trends.
- As a result, this value of '47 mg/dL' became widely accepted as the standard numerical value to define neonatal hypoglycemia for all infants, even healthy, term, appropriate for gestational age infants.
- It is clear that extremely low blood glucose concentrations in neonates can cause apnea, irritability, lethargy, seizures, and brain damage; and that prolonged or symptomatic hypoglycemia may correlate with long-term neurodevelopmental deficits.
- However, the long-term significance of early, asymptomatic and transiently low glucose levels remain not well established.
- And the evidence to support a clear numerical value of blood glucose that is associated with brain injury or reliably predicts adverse neurodevelopmental outcomes is lacking.
- Even Lucas et al. acknowledged that 'the association between [blood glucose concentrations <47 mg/dL] and poor neurodevelopmental outcomes might not be causal and might reflect a failure to adjust for confounding factors.'

Etiology

- Healthy infants experience an expected drop in blood glucose concentrations immediately following birth as a part of the normal physiologic transition to extrauterine life.
- Abruptly clamping the umbilical cord at birth disrupts the infant's connection to the placenta, upon which it relied to supply glucose and other metabolites necessary to meet its energy needs in utero.
- The continuous supply of exogenous intravenous glucose from the placenta suddenly ceases, and the infant's blood glucose concentration declines in the first hours of life.
- For most healthy infants, this transitional neonatal hypoglycemia is brief, transient and most often asymptomatic.
- Infants are at risk for more severe or prolonged hypoglycemia due to one or a combination of the following underlying mechanisms:
    - insufficient glucose supply, with low glycogen or fat stores or poor mechanisms of glucose production;
    - increased glucose utilization caused by excessive insulin production or increased metabolic demand;
    - or the failure of counter-regulatory mechanisms (i.e., pituitary or adrenal failure).
- Neonatal hypoglycemia most commonly affects the following groups of infants:
    - Intrauterine growth restriction or small compared to gestational age infants
    - Infants of diabetic mothers or large for gestational age infants
    - Late-preterm infants (34 to 36.6 weeks gestational age)
- Preterm, intrauterine growth restricted and small for gestational age infants are at risk for hypoglycemia because they are born with decreased glycogen stores, decreased adipose tissue and experience increased metabolic demands because of their relatively large brain size.
- In very low birth weight (<1000 g) preterm infants, the enzymes involved in gluconeogenesis are expressed at low levels; thus their ability to produce endogenous glucose is poor, contributing to their risk of severe or prolonged low glucose concentrations.
- Infants of diabetic mothers (IDM) and large for gestational age infants experience fetal hyperinsulinism and increased peripheral glucose utilization, putting them at risk for hypoglycemia in the immediate postnatal period.
- The placenta supplies the fetus with a direct source of glucose via facilitated diffusion, such that fetal glucose concentrations are proportional to maternal levels.
- Prolonged elevations in maternal glucose concentrations result in fetal hyperglycemia and pancreatic overstimulation to increase endogenous fetal insulin production.
- These elevated levels of fetal insulin persist after birth and, in the absence of a continuous exogenous glucose source, result in increased glucose utilization and lower blood glucose concentrations.
- IDM have a decreased ability to mobilize glycogen stores after birth and experience a relative adrenal insufficiency with decreased levels of catecholamines, further contributing to the risk of low blood glucose levels.

- Infants experiencing perinatal stress (e.g., fetal distress, perinatal ischemia, maternal preeclampsia/eclampsia, sepsis, hypothermia) or those with congenital heart disease have increased metabolic energy requirements, which puts them at risk for hypoglycemia.
- Perinatal stress causes a state of 'hypoglycemic hyperinsulinism' that can persist for days to weeks, resulting in persistently low glucose concentrations requiring ongoing interventions to maintain euglycemia.
- Other iatrogenic causes of transient neonatal hypoglycemia include intrapartum administration of maternal medication (e.g., beta-adrenergic tocolytic agents, valproic acid, propranolol, and conduction anesthetics), delayed feeding, and exogenous insulin administration.
- Low glucose concentrations beyond the first 48 hours of life raise concern for an underlying disorder as the etiology of hypoglycemia.
- The underlying physiologic mechanisms that cause pathologic or persistent hypoglycemia are similar to those described above:
    - hyperinsulinism (e.g., congenital hyperinsulinism, Beckwith-Wiedmann syndrome, Soto syndrome),
    - insufficient energy supply (i.e., inborn errors of metabolism that result in deficiencies in glycogen, amino acids, or free fatty acids),
    - or a deficiency in cortisol or growth hormone (e.g., Costello syndrome, hypopituitarism, congenital adrenal hyperplasia).
- Causes of persistent neonatal hypoglycemia include :
    - Congenital hyperinsulinism
    - Congenital syndromes: Beckwith-Wiedemann syndrome, Soto syndrome, Costello syndrome
    - Endocrine disorders: congenital hypopituitarism, congenital adrenal hyperplasia, hypothyroidism
    - Inborn errors of metabolism: maple syrup urine disease, glycogen storage disorders, hereditary fructose intolerance, galactosemia, fatty acid oxidation disorders

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Epidemiology

- The reported incidence of neonatal hypoglycemia is variable, depending on several factors: the population of infants included, the frequency and timing of glucose testing, the method of testing, and the definition of hypoglycemia used.
- A 2006 study by Harris et al. that sought to determine the incidence of hypoglycemia (blood glucose <47 mg/dL) in the first 48 hours of life in infants greater than 35 weeks gestation at risk of hypoglycemia by AAP guidelines found that 25% of all deliveries were at risk for hypoglycemia; of those at-risk infants, 51% experienced at least one episode of hypoglycemia.

Pathophysiology

- The fetus depends on maternal metabolism and placental circulation to provide the glucose, ketones, free fatty acids, and amino acids necessary to meet its energy requirements.
- The placenta supplies fetal circulation with a direct source of glucose.
- Clamping the umbilical cord at birth abruptly disrupts this continuous source of glucose, resulting in a rapid decline in blood glucose levels in the first 2 to 3 hours of life.
- Low blood glucose concentrations cause a surge of insulin and other hormones (including catecholamines, glucagon, and corticosteroids) that stimulate glucose production via gluconeogenesis and glycogenolysis and enhance fatty acid oxidation.
- This provides the infant with an endogenous source of glucose and other energy substrates necessary to sustain its metabolism ; the result is the gradual rise of blood glucose levels over the next several hours to days.
- Low glucose levels are also thought to stimulate the neonate's appetite and help the neonate adapt to intermittent feeds.
- Any mechanism that disrupts this sequence of physiologic changes puts the infant at risk of more severe or prolonged periods of low glucose.
- The risk for hypoglycemia is greatest in the first hours after birth.
- Persistent hypoglycemia results from excessive insulin secretion, a deficiency of cortisol or growth hormone, or inborn errors of metabolism.

History and Physical

- The clinical presentation of neonatal hypoglycemia is variable.
- An otherwise healthy infant may remain asymptomatic despite extremely low blood glucose levels during the period of transitional hypoglycemia.
- Clinical symptoms do not correlate with blood glucose levels.
- Symptoms of neonatal hypoglycemia include :
    - Sweating
    - Feeding difficulties, poor suck
    - Weak or high-pitched cry
    - Tremors
    - Hypothermia
    - Irritability
    - Lethargy/stupor
    - Hypotonia
    - Seizures
    - Coma
    - Apnea, grunting or tachypnea
    - Cyanosis

Evaluation

- The two major academic societies, the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES), present conflicting guidelines for screening at-risk infants and the management of neonatal hypoglycemia.
- The most recent AAP guidelines recommend screening for late preterm and term infants that experience symptoms of hypoglycemia, and asymptomatic infants at highest risk for hypoglycemia in the first 12 to 24 hours of life.
- "At risk" infants include late preterm (34-36.6 weeks gestation), term infants who are small for gestational age, infants of diabetic mothers, and large for gestational age infants.
- The guidelines state that 'routine screening and monitoring of blood glucose is not needed in healthy term infants after a normal pregnancy and delivery.'
- The Pediatric Endocrine Society (PES) recommends screening all infants with risk factors for prolonged or pathologic hypoglycemia, including :
    - Symptomatic hypoglycemia
    - Large for gestational age
    - Perinatal stress
        - Perinatal hypoxia/ischemia, fetal distress
        - Maternal pre-eclampsia/eclampsia
        - Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia
    - Premature or post-term delivery
    - Infant of diabetic mother
    - Family history of genetic hypoglycemia
    - Congenital syndrome (e.g., Beckwith-Wiedermann), abnormal physical features (e.g., midline facial malformations)
- Per the PES guidelines, infants unable to maintain pre-prandial blood glucose values >50 mg/dL in the first 48 hours of life or >60 mg/dL thereafter are at risk for persistent hypoglycemia and require further workup prior to discharge home.
- The PES recommends that the evaluation of infants at risk for persistent hypoglycemia for an underlying etiology occur after the first 48 hours of life, to exclude those infants experiencing transient low glucose levels (i.e., transitional neonatal hypoglycemia).
- The PES recommends evaluation of the following infants to exclude persistent causes of hypoglycemia :
    - Symptomatic hypoglycemia or severe hypoglycemia requiring treatment with intravenous dextrose
    - Infants unable to maintain blood glucose concentrations >50 mg/dL in the first 48 hours of life and >60 after 48 hours of age
    - Family history of a genetic form of hypoglycemia
    - Congenital syndrome (e.g., Beckwith-Wiedermann), abnormal physical features (e.g., midline facial malformations)
- Point-of-care testing (POCT) offers a quick and cost-effective method for screening for hypoglycemia.
- However, these methods have limitations.
- Most standard instruments use non-enzymatic methods to measure blood glucose concentration, which are less accurate at lower glucose values than laboratory analysis using glucose oxidase methods (the gold standard).

- Whole blood samples (used in POCT) have 10% to 18% lower glucose concentrations than plasma, depending on the hematocrit.
- Therefore, abnormally low glucose values on POCT require confirmation by measuring plasma glucose concentration using clinical laboratory methods.
- More recently, the use of continuous glucose monitoring (CGM) in the detection and management of neonatal hypoglycemia is under investigation.
- A study published in 2010 by Harris et al. looked at the usefulness of continuous glucose monitoring in 102 infants >32 weeks gestation at risk of hypoglycemia during the first 7 days of life.
- Infants were screened for hypoglycemia with intermittent blood glucose measurements and started on early oral feeds or intravenous dextrose solution per clinical guidelines.
- Investigators found that detected hypoglycemia (blood glucose <47 mg/dL) was present in 44% of infants using continuous glucose monitoring, versus 32% of infants with intermittent blood glucose sampling.
- And that there is good agreement between interstitial (used in continuous monitoring) and blood glucose measurements.
- The study suggests that continuous glucose monitoring is a safe, easy to use, and detects more episodes of hypoglycemia.
- In infants with persistent hypoglycemia suspected of having an underlying disorder, measuring bicarbonate, lactic acid, beta-hydroxybutyrate, free fatty acids, insulin and carnitine levels during hypoglycemia (blood glucose <50 mg/dL) is useful in differentiating between the metabolic causes of persistent hypoglycemia and aids in the diagnosis of hyperinsulinism and disorders of fatty acid oxidation.

Treatment / Management

- In the absence of a consistent definition of neonatal hypoglycemia, recommendations differ as to the lower level of glucose that is acceptable and when intervention is necessary.
- Though strategies focus on target glucose concentrations, the ultimate goal of management is to reduce the risk of brain injury and long-term neurodevelopmental deficits that may correlate with hypoglycemia.
- Early initiation of breastfeeding is crucial for all infants.
- For asymptomatic infants at risk of neonatal hypoglycemia, the AAP recommends initiating feeds within the first hour of life and performing initial glucose screening 30 minutes after the first feed.
- The AAP recommends goal blood glucose levels equal to or greater than 45 mg/dL prior to routine feedings, and intervention for blood glucose <40 mg/dL in the first 4 hours of life and <45 mg/dL at 4 to 24 hours of life.
- The best intervention for asymptomatic hypoglycemia is to increase feeding frequency.
- Increasing breastfeeding is challenging for some infants.
- Difficulties with infant latching, poor feeding, and low volumes of breast-milk may interfere with the successful establishment of early breastfeeding in the first hours of life.
- Most commonly, infant formula is the choice for asymptomatic neonatal hypoglycemia in late preterm and term infants.

- Formula is inexpensive, readily available, easy to give, and has a high carbohydrate content, resulting in a rapid rise of blood glucose concentrations within minutes.
- However, the use of infant formula risks interrupting establishment of breastfeeding and alters the neonatal microbiome, potentially increasing the risk of infections and allergies.
- Blood glucose levels should be re-checked one hour after feeding.
- It is uncertain whether early episodes of low glucose in the first 48 hours of life need correction in asymptomatic, healthy infants without risk factors for hypoglycemia.
- Dextrose gel 200 mg/kg massaged into the buccal mucosa is an effective treatment alternative in asymptomatic late preterm and term infants.
- Dextrose gel is relatively inexpensive, well tolerated, and its use has been shown to decrease admissions to neonatal intensive care unit for intravenous dextrose.
- Additionally, the use of dextrose gel may be a more advantageous treatment option over infant formula because it promotes breastfeeding and maternal-infant bonding.
- The AAP recommends admission to the neonatal intensive care unit and intervention with intravenous dextrose for the following:
    - All symptomatic infants with a glucose level less than 40 mg/dL
    - Infants with persistent hypoglycemia despite increased feeding frequency
    - ***Asymptomatic at-risk infants with extremely low blood glucose concentrations <25 mg/dL in the first 4 hours of life or <35 mg/dL at 4 to 24 hours of life.
- Intravenous glucose is given as a bolus of 200 mg/kg (dextrose 10% at 2 mL/kg), followed by continuous infusion of dextrose 10% at 5 to 8 mg/kg per minute (80 to 100 mL/kg per day) to maintain blood glucose levels of 40 to 50 mg/dL.
- Infants on intravenous dextrose infusions require close monitoring with frequent measurements of blood glucose levels, as often as every hour for the first 12 hours, then less frequently one target glucose values are achieved.
- In infants of diabetic mothers, lower glucose infusions rates of 3 to 5 mg/kg/minute may be used to minimize pancreatic stimulation and endogenous insulin secretion.
- Infants requiring higher rates of intravenous dextrose (>12 to 16 mg/kg/minute) or for more than 5 days are more likely to have a persistent cause of hypoglycemia.
- Second-line therapies for the treatment of persistent hypoglycemia include the use of corticosteroids or glucagon.
- Corticosteroids increased blood glucose concentrations by decrease peripheral utilization of glucose and are given as hydroxycortisone 5 to 15 mg/kg per day or prednisone 2 mg/kg per day.
- Glucagon is a hormone that stimulates endogenous glucose production via glycogenolysis and gluconeogenesis; thus its effectiveness depends on the infant having adequate glycogen stores.
- It is most useful in term infants and infants of diabetic mothers.
- Glucagon dosing is as a 30 mcg/kg bolus or 300 mcg/kg per minute continuous infusion.
- The PES recommends target glucose concentrations >50 mg/dL for infants at risk of hypoglycemia without a suspected congenital disorder during the first 48 hours of life, and >60 mg/dL thereafter.
- Infants unable to maintain these glucose targets despite regular feedings schedule should be evaluated to exclude a persistent cause of hypoglycemia prior to discharge home to ensure early recognition and facilitate treatment.

- For infants with persistent hypoglycemia, the goal of management in infants with suspected hyperinsulinism is to prevent recurrent episodes of low blood glucose levels that put the infant at risk for future episodes of hypoglycemia.
- For neonates with inborn errors of metabolism and impaired endogenous glucose production, the goal of management is to prevent metabolic acidosis and subsequent growth failure.
- The Pediatric Endocrine Society recommends giving endogenous glucose to keep blood glucose levels >70 mg/dL in these infants.
- Diazoxide infusions of 10 to 15 mg/kg per day may be used in infants with congenital hyperinsulinism to inhibit insulin secretions; effects are seen within 2 to 4 days.
- Recommendations call for early consultation with endocrinology or genetics.

Differential Diagnosis

- The symptoms of neonatal hypoglycemia are nonspecific and overlap with symptoms of other conditions, including prematurity, sepsis, hypoxic-ischemic encephalopathy and hyponatremia.
- As discussed above, though rare, persistent causes of hypoglycemia must be excluded.

Prognosis

- The implications of asymptomatic hypoglycemia in the first 48 hours of life on long-term neurodevelopmental outcomes remains bot well established.
- As a result of an influential study published in 1988 by Lucas et al. suggesting that recurrent, moderate neonatal hypoglycemia correlated with serious motor and mental impairments at 18 months corrected age, it was accepted that even early, asymptomatic hypoglycemia could harm long-term development.
- Several other observational studies presented similar conclusions.
- However, it is difficult to prove causation in observed outcomes.
- Contributing to the challenge in understanding the effects of low glucose levels, most studies have failed to include euglycemia controls and use variable definitions of 'hypoglycemia.'[2]
- A 2006 systematic review assessing the evidence of neonatal hypoglycemia on neurodevelopmental outcomes by Boluyt et al. found that a majority of studies were of overall poor quality and that the results of the two high-quality studies were invalid because of heterogeneity in methods.
- The authors' conclusion was that none of the studies provided valid evidence of the effects of neonatal hypoglycemia on neurodevelopment on which to make clinical recommendations and called for a well-designed, prospective study on this topic.
- Despite requests for further research of infants at risk of hypoglycemia with long-term neurodevelopmental follow up, there have only been two studies that meet the methodological criteria recommended by Boluyt et al.: A 15-year follow-up study of

recurrent hypoglycemia in preterm infants by Tin et al. and The Children with Hypoglycemia and Their Later Development (CHYLD) study.

- Published in 2012, the Tin et al. study sought to confirm the findings of the 1988 Lucas et al. study.
- This prospective study included preterm infants <32 weeks gestation born between 1990 and 1991 who had blood glucose measurements taken in the first 10 days of life.
- Investigators matched infants that had experienced recurrent neonatal hypoglycemia (defined as blood glucose <47 mg/dL on 3 or more days in the first 10 days of life) with euglycemia controls and found no differences in development or physical disability at age 2 years.
- On reassessment at age 15 years, investigators again found no difference in development or IQ scores between the two groups.
- The authors concluded that the "study found no evidence to support the belief that recurrent low blood glucose levels in the first 10 days of life usually pose a hazard to preterm infants".
- The CHYLD study is a prospective cohort investigation of infants born >32 weeks gestation with risk factors for neonatal hypoglycemia.
- The initial findings showed that treatment of neonatal hypoglycemia to maintain blood glucose >47 mg/dL did not correlate with an increased risk of neurosensory impairment at 4.5 years of age.
- Infants that experienced more severe or prolonged episodes of low blood glucose did not have worse outcomes.
- Investigators could not establish a numerical glucose level at which risk increased, but found that glucose instability (the proportion of measurements and duration of time blood glucose values were outside the range of 54 to 72 mg/dL) in the 48 hours of life was most predictive of worse developmental outcomes.
- Infants with the greatest glucose instability had a 2 to 3-fold increased risk of neurosensory impairment.
- Interestingly, moderate "hyperglycemia," blood glucose values >72 mg/dL, did correlate with an increased risk of poor visual motor and executive functioning.
- This finding raises the question: are infants experiencing low and "high" early blood glucose values at risk of worse neurodevelopmental outcomes?

Complications

- Severe, prolonged hypoglycemia in the neonatal period can have devastating outcomes, including long-term neurodevelopmental disabilities, cerebral palsy, and death.
- Infants with congenital causes of persistent hypoglycemia have significantly higher rates of morbidity and mortality: 25 to 50% have developmental disabilities.
- Nervous tissue can survive long periods of low blood glucose levels by utilizing alternative energy substrates (ketones, amino acids, lactate) to fuel its metabolic demands.
- The hypothesis is that the utilization of these alternative metabolites may have a neuroprotective effect on the immature neonatal brain.
- Ultimately, however, a glucose supply must be established.

- In 1967, Anderson et al. published a case series of the pathologic findings of 6 infants with severe, prolonged hypoglycemia in the first week of life.
- The authors reported that severe, prolonged hypoglycemia caused extensive degeneration of the central nervous system and, if left untreated, ultimately resulted in death.
- The brain damage was less severe in infants treated with exogenous glucose.
- Thus, early recognition of conditions that cause persistent hypoglycemia is critical.
