

Hypoglycemia in the preterm neonate: etiopathogenesis, diagnosis, management and long-term outcomes

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Abstract: Glucose, like oxygen, is of fundamental importance for any living being and it is the major energy source for the fetus and the neonate during gestation. The placenta ensures a steady supply of glucose to the fetus, while birth marks a sudden change in substrate delivery and a major change in metabolism. Hypoglycemia is one of the most common pathologies encountered in the neonatal intensive care unit and affects a wide range of neonates. Preterm, small for gestational age (GA) and intra-uterine growth restricted neonates are especially vulnerable due to their lack of metabolic reserves and associated co-morbidities. Nearly 30–60% of these high-risk infants are hypoglycemic and require immediate intervention. Preterm neonates are uniquely predisposed to developing hypoglycemia and its associated complications due to their limited glycogen and fat stores, inability to generate new glucose using gluconeogenesis pathways, have higher metabolic demands due to a relatively larger brain size, and are unable to mount a counter-regulatory response to hypoglycemia. In this review we will discuss the epidemiology; pathophysiology; clinical presentation; management and neurodevelopmental outcomes in affected infants and summarize evidence to develop a rational and scientific approach to this common problem.

Keywords: Hypoglycemia; gluconeogenesis; hypoglycemic brain injury; neurodevelopmental outcome; intra-uterine growth restriction

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Introduction

Hypoglycemia [Gk. hypo (below or under) + glykys (sweet) + haima (blood)] meaning a decreased level of sugar in the blood was coined by Harris in the late 19th century (1). Over the last century there has been a large body of literature looking into the effects of low blood glucose, specifically on neonates, however there is little consensus regarding its definition or acceptable range of glucose in various types of neonates. Hypoglycemia has since been measured and defined as a range of clinical manifestations and lab values and approach to this problem has slowly

been tailored to the particular infant's unique physiologic adaptations. The association of hypoglycemia and neurodevelopmental abnormalities in preterm infants was first defined as early as 1937. This led to categorization of hypoglycemia as “mild” between 40 to 50 mg/dL (2.2 to 2.8 mmol/L), “moderate” between 20 and 40 mg/dL (1.1 to 2.2 mmol/L) and “severe” as 20 mg/dL (1.1 mmol/L) (2). One group of investigators suggested 30–35 mg/dL (1.67 to 1.94 mmol/L) as the normal low range of glucose during the first 24 hours of life; 45 mg/dL (2.5 mmol/L) after feeding and 40–50 mg/dL (2.22 to 2.78 mmol/L) after completion of 24 hours of life (3). Since then,

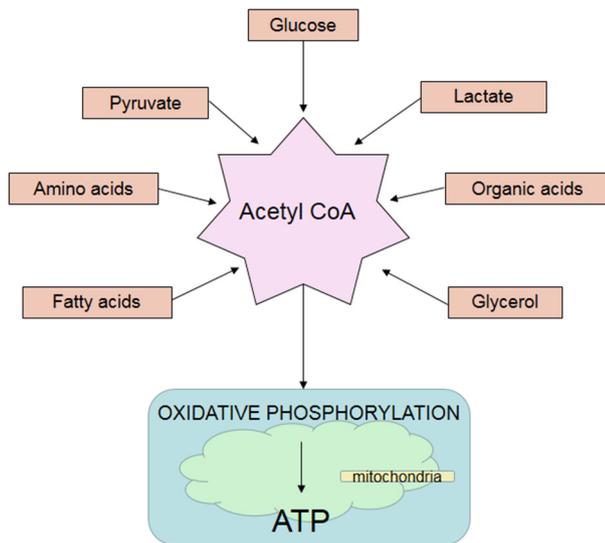


Figure 1 Mechanisms which generate acetyl CoA, the metabolic common currency which determines ATP levels and clinical presentation. ATP, adenosine triphosphate.

many operational thresholds have been described. The American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) have both tried to come to a consensus for a safe range of glucose in neonates. It is now accepted that plasma glucose values drop down to 30 mg/dL (1.67 mmol/L) in the first 2 hours of life and subsequently rise to a value of at least 45 mg/dL (2.5 mmol/L) before stabilizing around 12–24 hours (4). The AAP has arbitrarily adopted the numerical plasma glucose value of 47 mg/dL (2.6 mmol/L) to define hypoglycemia in neonates (5).

Small for gestational age (GA) neonates and preterm infants

Studying energy requirements specifically glucose, in both small for gestational age (SGA) and appropriate size for gestational age (AGA) preterm infants has been a topic of interest for the last many decades. Initial studies dating back to the early 1970's confirmed the belief that not only are these infants more susceptible to lower blood glucose values, but they are also at higher risk for slow recovery and poor long-term prognosis (6,7). The estimated incidence of hypoglycemia in SGA infants is around 70% (8). One study showed that 15% of preterm hypoglycemic infants were AGA and the rest were either large for gestational age

(LGA) or SGA (9). In 1970's, Cornblath *et al.* put forth the possibility of a lower operational threshold of blood sugar for preterm infants at 20 mg/dL based on the rationale that their being symptom free proved that their brains are less susceptible to and better adapted to low glucose values (3). Transabdominal cordocentesis was done to measure fetal blood glucose values and then compared with maternal serum glucose concentration, showed fetal venous glucose values of 72–90 mg/dL (4–5 mmol/L). There was a widening of glucose gradient between maternal and fetal circulation as the infant approached term (10). It has been shown that intra-uterine growth restriction correlated closely with the degree of hypoxia but not hypoglycemia. The hypoglycemia itself is more a result of decreased production of glucose due to small stores of glycogen than excess utilization (11). There is a strong correlation between fetal and maternal glucose values during early gestation. However, approaching the third trimester, with increased fetal glucose utilization, the gradient increases and maternal values are higher than fetal values (12). This suggests that preterm and SGA infants should characteristically have similar serum glucose concentration as their mothers. In order to promote facilitated diffusion in severely growth restricted fetuses, this gradient is widened and is a function of clinical severity, hence, fetal blood glucose values correlate with GA as well as maternal glucose (13).

Physiology of glucose metabolism in the neonate

A steady state glucose level is maintained by various processes of gluconeogenesis, metabolism, insulin secretion, and 'counter regulatory' hormones in the neonate as shown in *Figures 1* and *2*. This homeostasis is maintained not only by insulin and glucagon but also by hormones such as catecholamines, growth hormone, and cortisol that determine its uptake and utilization. Ingestion of feed or infusion of glucose in the form of carbohydrate contributes to increasing glucose concentration in the body which in turn activates glucokinase and β cell glycolysis (14,15). This process eventually generates acetyl-coenzyme A (acetyl CoA) which is a common end product not only of glycolysis but also of protein degradation and lipolysis. Acetyl Co-A enters the Krebs's cycle which then provides the adenosine triphosphate (ATP) and supports all cell functions (15,16).

Pancreatic β cells produce insulin and α cells produce glucagon. β cells contain ATP-sensitive potassium channels (also known as K_{ATP} channels which contain two subunits:

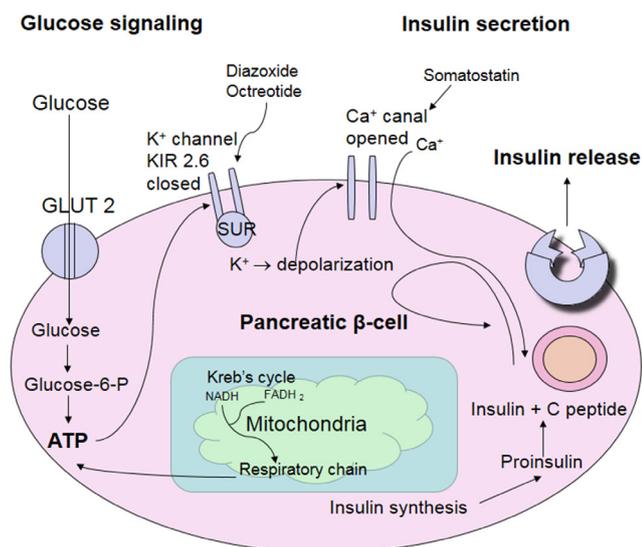


Figure 2 Molecular machinery which controls Insulin secretion by the pancreatic β cells.

sulfonylurea [sulfonylurea receptors (SUR)] and an inward rectifier potassium channel (Kir6.2) (14,16). ATP produced as a result of the citric acid cycle closes the K_{ATP} channels simultaneously creating an inflow of calcium through voltage gated calcium channels that leads to release of insulin (17) (Figure 2). If there is paucity of glucose in the blood; glucagon is secreted, possibly due to a similar mechanism via K_{ATP} channels on the α cells.

Facilitated transport of glucose

Glucose is the major source of energy for the brain, fetal and neonatal brains are capable of utilizing ketone bodies, lactate and even amino acids in extreme conditions (3,18). The neonatal brain is one of the most energy efficient organ as it oxidizes almost all of the glucose delivered to it (19). Glucose transport (GLUT) through the blood-brain barrier as well as its permeation through lipid membranes of neurons and glia takes place through a process known as facilitated diffusion. Facilitated diffusion is an energy independent pathway that transports glucose from blood into the cytoplasm and the process is bidirectional. Thus, ongoing glycogenolysis and gluconeogenesis often contribute to efflux of glucose from the cell.

During gestation, in mature placentas, insulin does not alter or assist glucose uptake from the maternal or fetal side (20). The large surface area of choriodecidual villi is

directly in contact with maternal blood resulting in the mother-baby dyad sharing a common pool of glucose (19,21). Most of the glycogen deposition in the fetal tissue occurs during the second half of pregnancy. Adequate transport of glucose from mother to baby is mainly determined by the umbilical blood flow since there has been no demonstrable difference in levels of expression of glucose transporter-1 (GLUT-1) protein in placentas (22).

GLUT proteins

Facilitated glucose transfer is mediated by a family of GLUT proteins, nearly 14 of which have been identified so far. Protein and mRNA levels of GLUT1 increase in the placenta with fetal maturation (23). It has been shown to be responsible for transfer of glucose, transporting it from maternal blood into the cytoplasm of the syncytiotrophoblast and then into the extracapillary space in the fetal circulation, by facilitating its exit through the basement membrane (21).

GLUT 1, 3 and 11 are found in the placenta and are important for the growing fetus while GLUT 2 and 4 are insulin responsive glucose transporters (20). GLUT 1 helps transport glucose across the blood brain barrier (BBB) and working closely with GLUT 3 assists in brain cell glucose uptake (24). GLUT's play a significant role in determining the phenotype of the large and small for GA infants. Gestational diabetes leads to increased glucose in the maternal blood and hence increased transplacental transport into the placenta and the fetus resulting in excess growth mediated through insulin like growth factor-1 (IGF-1). In these pregnancies GLUT 1 levels were found to be elevated while no changes were found in GLUT 3 and GLUT 4, suggesting that fetal hyperglycemia in diabetic pregnancies is a direct correlate of GLUT 1 levels. In animal studies of IUGR pregnancies, there has been an observed relative fetal hypoglycemia which further enhances facilitated diffusion (20,21,25-28).

Physiology of transition from fetal to the neonatal life

Transition from fetal to the neonatal life is the most complex and crucial physiological adaptation in human life (29,30). As the placental supply of glucose ceases, the plasma glucose values hit a nadir in the first 2 hours after birth triggering release of counter regulatory hormones important for gluconeogenesis within the first 6–24 hours

of life (31). There is a surge in catecholamines (epinephrine and norepinephrine), which play a crucial role in adaptation to various stressors outside the womb (29,32). Infants born via cesarean section have lower catecholamine levels compared to those born via spontaneous vaginal delivery and therefore are more prone to developing hypoglycemia. Paradoxically some preterm infants have higher cord blood levels of catecholamines compared to term infants (29). Catecholamines assist in maintaining blood pressure, and normothermia by stimulating alpha receptors which then increase blood pressure and helps utilize brown fat. This also helps prevent hypoxia by induction of alveoli to increase surfactant production (29). Epinephrine promotes liver glycogenolysis and gluconeogenesis which helps prevent hypoglycemia (33).

A “cortisol surge” occurs along with catecholamine release, promoting increased β receptor density in blood vessels and increases gluconeogenesis which further raises serum glucose levels (29,34). Preterm infants (33–36 weeks GA) have been shown to have higher cortisol blood levels than term infants (35) but levels in preterm infants 24–36 weeks GA are inversely proportional to the gestation and tend to remain high from day of life 2 through 6. However, infants <28 weeks GA and extremely sick infants do not demonstrate the same response thus making them more vulnerable to hypoglycemia (36).

Etiopathogenesis of hypoglycemia

Hypoglycemia essentially results from either decreased production or excessive utilization of glucose reserves. Thus, hypoglycemia occurs in a neonate who is born with low glycogen and fat stores with limited capacity to generate glucose via the gluconeogenesis pathway or excessive peripheral tissue utilization of glucose like in an infant of a mother with insulin dependent diabetes (37–39). Euglycemia after birth is maintained by a combination of finely controlled metabolic adjustments and hormone secretions. Extremely low-birth weight (ELBW) preterm neonates are born with low stores of glycogen and adipose tissues. This situation is further complicated by the fact that several enzymes involved in gluconeogenesis viz. Phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase, fructose-1,6-diphosphatase, and Pyruvate carboxylase are expressed at very low levels limiting their capacity for gluconeogenesis. Preterm infants and those with IUGR are highly likely to become hypoglycemic in the immediate neonatal period (40). Various congenital disorders such as Beckwith-Wiedemann syndrome, Turner

syndrome, Down syndrome, Costello syndrome, congenital hypopituitarism, and congenital adrenal hyperplasia also predispose the infant to hypoglycemia. Inborn errors of metabolism like maple syrup urine disease, glycogen storage disorders, fructose intolerance, and fatty acid enzyme deficiencies can also result in persistent hypoglycemia.

Neonates have a poorly developed counterregulatory mechanisms to counter hypoglycemia which makes them highly vulnerable. The hypoglycemic neonate defends itself by decreasing insulin secretion and increasing glucagon, epinephrine, growth hormone, and cortisol secretion which leads to glucose production & mobilization of fatty acids from adipose tissues. The increase in glucose production comes initially from the breakdown of glycogen (up to 1–2 h) and later there is protein breakdown with increasing levels of cortisol. This process is evident by increased plasma levels of gluconeogenic amino acids, alanine, and glutamine. Hypoglycemia occurs when there is excessive production of insulin (overutilization), poor gluconeogenesis (underproduction), or failure of counterregulatory mechanisms (pituitary or adrenal failure).

Approach to diagnosis and management of hypoglycemia in the preterm infant

The diagnosis and management of hypoglycemia depends mostly on the cause and severity of hypoglycemia, the clinical presentation and the underlying etiology. Thus, the treatment plan should be individualized for each infant (*Figure 3*). The Whipple’s triad of clinical signs, low glucose value, and resolution of signs on treatment (38,41) was utilized in the past but lately we have moved more towards a proper definitive biochemical diagnosis. The key to diagnosis is to determine whether the hypoglycemia is likely to be transient or persistent (*Table 1*). Based on that determination, one should refer an infant with persistent hypoglycemia to a tertiary center and order sophisticated investigation as outlined below.

The infant can present with either neurogenic or neuroglycopenic signs and symptoms of disease. Neurogenic refers to an active catecholamine based response involving, tachycardia, vomiting, sweating, tremors, vomiting. Neuroglycopenic signs manifest as a result of neuronal deprivation of glucose presenting as hypotonia, apnea, seizures with coma being the worst outcome (43). Biochemical estimation of blood glucose values is more accurate than clinical assessment alone. Plasma glucose values are higher than whole blood values by 10–18% (4).

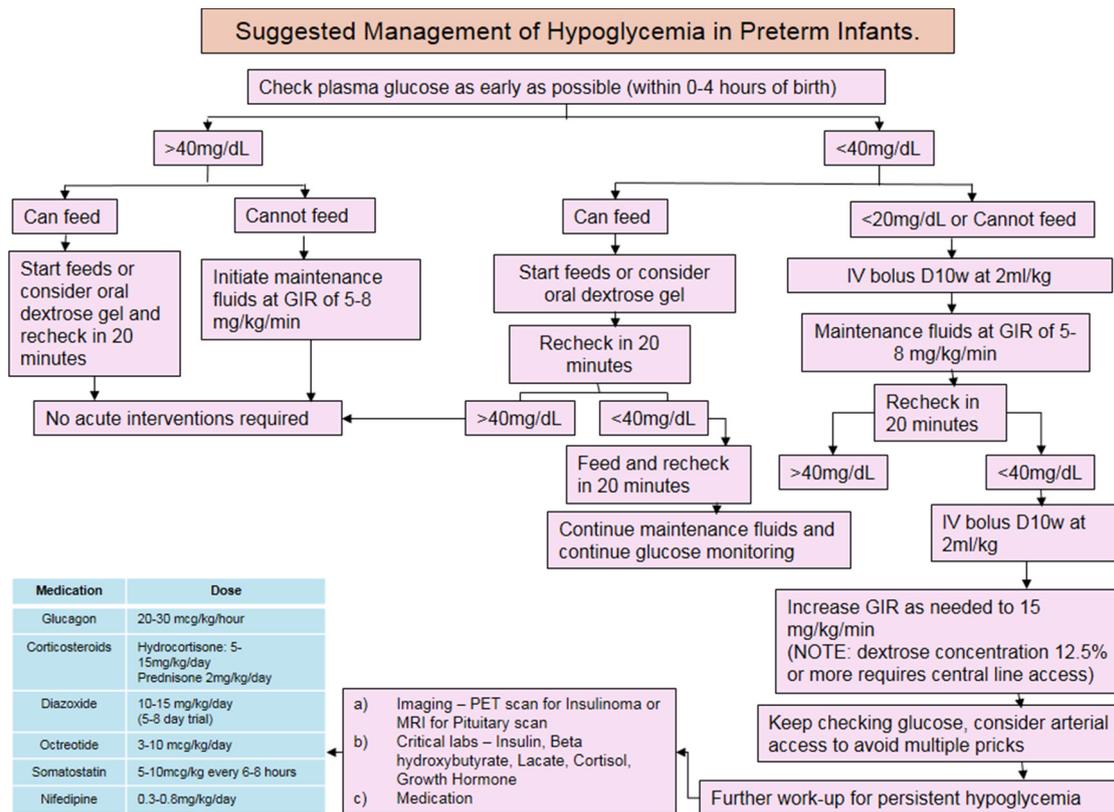


Figure 3 Suggested algorithm for management of hypoglycemia in the preterm infant.

The Pediatric Endocrine Society (PES) and the American Academy of Pediatrics (AAP) recommend a glucose level of ≥ 40 mg/dL (mmol/L) in the first 4 hours; ≥ 45 mg/dL (mmol/L) after feeding at 4–24 hours and treat values of ≤ 40 mg/dL (mmol/L) parenterally (15,19,44). The PES recommends a similar strategy suggesting levels of >50 mg/dL (mmol/L) in first 48 hours and >60 mg/dL (mmol/L) thereafter (19).

Persistent hypoglycemia is a medical emergency and calls for a fast action where a delay will lead to complications and blood glucose needs to be maintained at >70 mg/dL (mmol/L) (19). Normal term infants should be fed where possible resulting in increase in blood glucose by 30 mg/dL (1.67 mmol/L) per 30–60 mL of standard infant formula. Blood glucose should continue to be evaluated before and after feeds for at least 12–24 hours. If normoglycemia is not attained, the next step is administration of parenteral dextrose, starting with the “mini bolus” approach of 200 mg/kg of 10% dextrose in water (2 mL/kg D₁₀W) followed by constant IV infusion and a recheck of blood sugar after 30 minutes later and then

hourly (15).

The goal is to provide a continuous glucose infusion rate (GIR) of 6–8 mg/kg/min (3), this is particularly important in preterm and low birth weight infants since it is equivalent to the sugar that would have been provided by the liver via gluconeogenesis (3,10,45). A lower dextrose infusion rate of 3–5 mg/kg/min may be used for infants born to mothers with diabetes to provide minimal stimulation to their pancreas to secrete insulin (19). With these interventions, if an infant does not attain normoglycemia it is prudent to go up on the GIRs to 8, 10, 12 and then 15 mg/kg/min over a period of 24 hours (3). A dextrose concentration of higher than 12.5% calls for central venous access (46). Obtaining arterial access may also be prudent in these infants to avoid repeated needle pricks to the fingers, toes and heels of these extremely preterm babies.

Continuous glucose monitoring (CGM), although still experimental, is emerging as the new standard of care for monitoring blood glucose in tiny babies. The CGM device measures and updates blood glucose values every 5 minutes, providing real time data (42,47). Once a reliable

Table 1 Causes of hypoglycemia (15,19,42)

Etiology	Pathology	Effect
Prematurity or perinatal distress	Prematurity, small for gestational age (SGA), perinatal events such as Asphyxia, intrauterine growth restriction (IUGR), sepsis	Transient
Syndromes	Growth hormone deficiency, Turner syndrome, congenital hypopituitarism, Costello syndrome, Down's syndrome, cortisol deficiency, congenital hypopituitarism, congenital adrenal hyperplasia	Persistent
Insulin excess	Infant of diabetic mother, congenital hyperinsulinism, familial hyperinsulinism, Beckwith-Wiedemann syndrome, Sotos syndrome	Transient/persistent
Metabolic disorders	Organic acidemias such as maple syrup urine disease (MSUD), glycogen storage disorders, hereditary fructose intolerance, galactosemia, fatty acid oxidation disorders	Persistent
Iatrogenic	Tocolytic administration in mother (beta adrenergic), hypothermia, asphyxia	Transient
Defects of glucose transporters	GLUT 1 and GLUT 2 deficiency	Persistent

means of evaluating the infant's blood glucose level has been established it is important to titrate dextrose infusion accordingly. With effective therapy, most infants attain euglycemia in 2–4 days. A period of 5–7 days of hypoglycemia points toward a diagnosis of persistent neonatal hypoglycemia and necessitates alternative therapies (46). The PES suggests consideration of persistent hypoglycemia after a period of 48 hours and recommends further work up. This includes laboratory tests like insulin level, a metabolic profile, genetic studies and imaging to look for pathology in the pancreas, adrenal and the pituitary glands (19).

Corticosteroids such as hydrocortisone at 5–15 mg/kg/day or prednisone at 2 mg/kg per day decreases peripheral utilization of glucose, thus remain the second line of treatment after starting glucose infusion for persistent hypoglycemia (3,48–51). Glucagon, produced by the α cells in the pancreas, is a counter regulatory hormone and initiates gluconeogenesis and glycogenolysis during hypoglycemia (52), is helpful in raising blood glucose when infant has adequate glycogen stores. However, its effectivity is limited in infants of mothers who were on beta blockers such as atenolol or metoprolol (53). Glucagon administered at 30 mcg/kg or 300 mcg/kg/min infusion in infants with adequate glycogen stores promotes glycogenolysis and gluconeogenesis (16). Glucagon is especially helpful for term infants, infant of diabetic mothers when short-term treatment is desirable like during transport of critically ill infants.

Somatostatin which inhibits insulin and growth hormone release is usually reserved as a last line of treatment when other therapies fail to raise and maintain blood sugar (48).

Octreotide, a long acting analogue of endogenously occurring somatostatin which acts directly on the voltage gated calcium channels has an inhibitory effect on insulin release is used where diazoxide (14,54). It is used as a constant infusion at 3–10 mcg/kg/day (14), however, it is not currently FDA approved and there are concerns that it impedes neonatal growth.

Hyperinsulinism related to genetic defects of SUR where there is unchecked production of insulin usually responds well to treatment with diazoxide (16,48). Diazoxide, a high affinity K_{ATP} channel opener acts by stabilizing these channels, and it blocks insulin secretion (55) thereby helping in the management of persistent hyperinsulinism. If hyperinsulinism is secondary to abnormalities in the SUR and Kir 6.2 subunits of the glucose channels, an impressive response to diazoxide may or may not be seen. Diazoxide is commonly used in the dose range of 10–15 mg/kg/day where responders show effect within 2–4 days (56).

Nifedipine is another off-label drug for neonatal use in cases where a response to diazoxide and octreotide are not seen (57). Nifedipine has been used in babies at a dose of 0.3–0.8 mg/kg/day by Bas *et al.* (58) and was effective when other therapies failed, but this medication is not the mainstay of treatment due to its cardiovascular side effects.

Newer approaches to management of neonatal hypoglycemia

Recently oral dextrose gel administration has been a very promising new intervention for management of neonatal hypoglycemia especially in the term, near term, or late

Table 2 Summary of dextrose gel treatment studies for hypoglycemia

Citation	Study design	Key findings	Comments
Weston <i>et al.</i> , 2017 (59)	N=211, hypoglycemic infants, randomized case control study	Pre-feed alertness scores were similar in babies treated with dextrose gel or placebo. Breastfed babies had good feeding scores and improved formula volumes	Dose of 200 mg/kg does not depress desire to feed; on the contrary may help in improved breastfeeding
Ter <i>et al.</i> , 2016 (60)	N=200 (100 each in pre- and post-dextrose gel group), prospective audit and cohort study	NICU admissions pre- and post-introduction of dextrose gel: 29% vs. 14%. No significant difference in achievement of normoglycemia in either group. Recurrence of hypoglycemia was higher in dextrose gel group (31% vs. 49%)	Over-all reduction in NICU admission and separation of mother from baby
Rawat <i>et al.</i> , 2016 (61)	N=250, hypoglycemic infants	Normoglycemia achieved in 74% of hypoglycemic infants on dextrose gel with feeds vs. only 58% infants on only feeds. Breast feeding rate (exclusive) increased from 19–28%	Decreased separation of mother and baby; promoting of bonding. Increased breastfeeding rates
Hegarty <i>et al.</i> , 2016 (62)	N=415, randomized double-blind placebo-controlled study	Dextrose gel (40% dextrose) at 200 or 400 mg/kg x3 compared to placebo. Incidence of hypoglycemia estimated at 186/415 (45%)	Babies on dextrose gel less likely to experience hypoglycemia. Recurrent hypoglycemia independent of dextrose gel. No difference in rates of admission to the NICU
Harris <i>et al.</i> , 2016 (63)	N=237, prospective cohort, follow-up of the sugar babies study	36% (n=66): neurosensory deficit (dextrose gel: 38%, placebo: 34%). Bayley III scoring: scores were 0.25–0.5 SD below standardized mean for the entire cohort	Dextrose gel is a safe and effective for neonatal hypoglycemia. Neurosensory deficit still possible
Harris <i>et al.</i> , 2013 (64)	N=514, the sugar babies study	242/514=47% infants were hypoglycemic. 3% babies in placebo group had a glucose concentration 0.9 mmol/L	Oral glucose gel, the first line of treatment in 48 h of life

preterm infants. Several studies have been conducted using dextrose gel and are summarized in *Table 2*. In the Sugar Babies trial, Harris *et al.* (64) were able to effectively show improvement in hypoglycemia within the first 48 hours; promote bonding, and prevent separation of mothers from the babies. The follow-up study conducted by the same group questioned the previous promising results by showing that it did not impact neurodevelopmental outcomes (63). Several studies have concluded that oral dextrose gel is suitable to treat hypoglycemia in stable infants, who can be fed (59–62). Dextrose gel is being favored not only for prevention and treatment of hypoglycemia but for promoting breast feeding and bonding of mothers and babies.

Neurodevelopmental outcomes after hypoglycemia

Neuroradiological studies to investigate the anatomical location of brain injury due to hypoglycemia specifically using various MRI techniques demonstrated cortical

abnormalities in the posterior cerebral cortex with or without subcortical or periventricular injury (65). There is sparing of the parietal and occipital lobes (66,67). In rare circumstances there can be thalamic involvement or injury to the basal ganglia as well. Therefore, follow-up MRI studies are indicated when there is history of prolonged and severe hypoglycemia (65). Hypoglycemic brain injury does not necessarily track the vascular supply, thus it may be possible at times to differentiate hypoglycemic from hypoxic brain injury (68). Neurodevelopmental outcomes in infants with hypoglycemia have been extensively reviewed and some of these studies are summarized in *Table 3* (8,69–78). Hypoglycemic brain injury may cause a long-term effect on the developing nervous system and may be the reason for developmental delay, cerebral palsy and other neuropsychiatric deficits noted in these children.

The Babies and Blood Sugars study (BABIES) studied influence of hypoglycemia on EEG using bed-side amplitude integrated electroencephalography (aEEG) to assess real-time neuronal injury due to hypoglycemia (79).

Table 3 Summary of studies detailing neurodevelopmental outcomes in hypoglycemia preterm infants

Citation	Study population	Study design and level of evidence	Outcomes	Key findings	Comments
Koivisto et al., 1972 (69)	N=151, convulsion (N=8), non-convulsion (N=77), asymptomatic (N=66), control (N=56)	Prospective cohort study, single center study	Followed through 4 years of age. Hypoglycemia lasted 105 hours in the symptomatic group with convulsions; 49 hours in the symptomatic non-convulsive and 37 hours in the asymptomatic. Toxemia was the most common maternal disease	12.9% SGA had sequelae, no pathologies in the asymptomatic group, 8.7% controls had abnormalities. Preterm infants with sequelae by group: symptomatic: 36.4% vs. 13.5% in term, asymptomatic: 22.2% vs. 3.7% in term, control: 12.5% (1/8)	Neonates with symptomatic hypoglycemia suffer consequences but asymptomatic neonates do not
Lucas et al., 1988 (70)	N=661 (<1,850 g), 433 glucose \leq 2.6 mmol/L, 222 infants were symptomatic	Multi-center prospective cohort study with similar early feeding practices	Mental and motor developmental scores at 18 months corrected gestational age (CGA)	Number of days (\geq 3–4) of hypoglycemia were directly proportional to degree of damage including cerebral palsy and global developmental delay. A difference of 13–14 points was seen on Bayley scores of infants with and without hypoglycemia at 18 months CGA	Moderate hypoglycemia poses significant neurodevelopmental damage and warrants close observation and treatment
Duvanel et al., (8)	Preterm (\leq 34 weeks), SGA ($<$ 10 th percentile), N=85	Prospective cohort study for growth and development, retrospective grouping according to glycemic status	Griffith's quotients used at CGA's of 6, 12 and 18 months respectively. An adaptation of scales of aptitude for children and McCarthy for the French-speaking families was used	Hypoglycemia in SGA: 73% (62/85). More events in moderate hypoglycemia 11/53 (21%) vs. 1/49 (2%) for severe (due to prompt treatment). Significant decrease in head circumference at 12 and 18 months CGA (P<0.001) and age 5 years. McCarthy's test: perceptible performance affected (after 1 episode) > motricity scale (after 7 episodes). Griffith's test: did not show any statistical difference	Hypoglycemia in SGA much more than previously known. Repeat episodes predictive of poor outcome. Neurodevelopmental effects persist well into 5 years of age
Filan et al., 2006 (71)	N=6 (1 with long chain fatty acid oxidation defect and another with perinatal asphyxia excluded)	Prospective cohort study	Early (D #4–7) and follow-up (D #11–50). Insulin, growth hormone and cortisol levels done. Developmental assessment done by pediatrician, and visual assessment by ophthalmologist	Seizures in 50% where Cranial US normal in 75%. MRI abnormalities included extensive areas of restricted diffusion within occipital cortex and white matter, corpus callosum and optic radiations along with involvement of the cerebral cortex. Deep nuclear grey matter was spared. At 1 year of age, 1 had evolving microcephaly, gross motor delay and visual impairment	Positive MRI findings

Table 3 (continued)

Table 3 (continued)

Citation	Study population	Study design and level of evidence	Outcomes	Key findings	Comments
Burns <i>et al.</i> , 2008 (72)	N=35 term (>36 wk) infants with symptomatic hypoglycemia (<1 mmol/L). Control N=229 term neurologically normal	Prospective cohort study	MRI of brain on all patients at median age 9 days. Neurodevelopmental outcomes assessed at 18 months of age using Griffith's Mental Development scales	MRI findings: white matter anomalies in 94%; severe in 43% and posterior injury in 29%. Cortical abnormalities in 51%; white matter hemorrhage in 30%, basal ganglia and thalamic lesions in 40%, abnormal posterior limb of internal capsule in 11%. Neurodevelopmental: 23.5% normal; 44% mild impairments, 23.5% moderate and 8.8% severe	Early MRI findings more suggestive of subsequent neurodevelopmental abnormalities. No striking differences in transient versus prolonged or recurrent hypoglycemia
Per <i>et al.</i> , 2008 (73)	N=93, 26 followed up. No evident abnormality on neuro exam	Retrospective cohort study	MRI performed at age range of 3 days–18 years	Occipital (n=20), parietal (n=2) and fronto-temporal (n=1) involvement noted on MRI examination	No relationship between neurologic sequelae OR MRI findings and glucose levels
Montassir <i>et al.</i> , 2009 (74)	N=60. Group I: mental retardation, developmental delay, cerebral palsy (n=12); group II: normal	Retrospective chart review	Enjoi development scale. Intellectual testing: Japanese Wechsler intelligence scale for children III (score of ≤ 80 : developmental delay or mental retardation)	10/12: developmental delay and mental retardation. 7/12: epilepsy. 5/12: status epilepticus. Maternal diabetes not noted in group I; noted in 2/48 in group II. Toxemia in 4/12 (33.3%) in group I; 3/48 (6.4%) in group II.	Severe and prolonged hypoglycemia results in neuronal injury. Injury exacerbated with hypoxia, seizures and hyperbilirubinemia
Kerstjens <i>et al.</i> , 2012 (75)	N=832, moderate pre-terms	Prospective cohort study	Ages and Stages Questionnaire (ASQ) filled out by parents when child attains 43–49 months of age	Prevalence of neonatal morbidities ranged from 1.1% to 4.6%. Hypoglycemia and asphyxia had a definite positive association when compared with the ASQ. Serum glucose <1.7 mmol/L (30 mg/dL) increased risk of developmental delay from 9.1% to 20%	Hypoglycemia is a significant risk factor for developmental delay in children belonging to pre-school age-group at 4 years of age
Tin <i>et al.</i> , 2012 (76)	N=566. Index children: 48/566 with serum glucose ≤ 2.5 mmol/L for ≥ 3 /first 10 days of life. 1 excluded due to myotonic dystrophy; n=47	Prospective cohort study	Developmental assessment at 2 years CGA with Griffiths scales for Mental Development. 45/47 children were followed at 15 years of age by a research psychologist. Full IQ testing using Weschler-III assessment tool. Vineland Adaptive Behavior Score was also used	18/47 had serum glucose <2.0 mmol/L on 3 separate days out of first 10. Mean IQ in 14/47 was 81.6 (± 20.1) vs. controls with 82.2 (± 20.7). 6 index and 8 controls had a Vineland score <60. 6 index and 4 controls had cerebral palsy. N-2 had an IQ of <70	No evidence to prove hazard to preterm infants due to recurrent low blood glucose (≤ 2.5 mmol/L)

Table 3 (continued)

Table 3 (continued)

Citation	Study population	Study design and level of evidence	Outcomes	Key findings	Comments
McKinlay et al., 2015 (77)	Children with Hypoglycaemia and Their Later Development (CHYLD) study. Gestational age at least 35 weeks N=404; 53% were hypoglycemic with blood glucose <2.6 mmol/L (47 mg/dL)	Prospective cohort study of term and late-preterm infants at risk of hypoglycemia. Study ran parallel to Babies and Blood Sugar's Influence on EEG Study (BABIES) & The Sugar Babies Study (oral dextrose gel)	Bayley Scales of Infant Development-III at 2 years CGA. The Behavior Rating Inventory of Executive Function- preschool version (BRIEF-p) survey was filled out by caregivers	Children with history of hypoglycemia had better Bayley scores (by 3.5 points; 95% CI, 0.40–6.5; P=0.02) for social and emotional adaptation than euglycemic infants. Undiagnosed untreated hypoglycemia led to neurosensory impairment (14/33 vs. 45/108). Longer duration of abnormal values correlated positively with cognitive delay but not language or motor delay. Higher glucose concentrations in first 48 hours showed direct correlation with impairment. Disability was directly proportional to the maximum glucose value in the first 12 hours	Risk of neurosensory delay was not increased in the hypoglycemic group. Incidental finding that neurosensory impairment was more pronounced in the group with hyperglycemia though uncommon (3 infants had blood glucose >8.0 mmol/L, 144 mg/dL)
Kaiser et al., 2015 (78)	23–42 weeks. N=1,395 (normoglycemia or transient hypoglycemia)	Retrospective cohort study	Measurement of literary and mathematics performance in school for a fourth grader on children 10 years of age	Test scores: literacy, 32% in hypoglycemic group vs. 57% in euglycemic group; mathematics, 46% vs. 64% in normoglycemic group	Early transient newborn hypoglycemia associated with lower school scores at age of 10 years

SGA, small for gestational age.

Levels of glucose as well as non-glucose cerebral fuels such as lactate, beta hydroxybutyrate and glycerol were measured. These studies showed no significant EEG abnormality even during periods of low glucose and use of alternate cerebral fuels hence demonstrating that aEEG was not a useful tool (79).

Normal brain obtains more than 50% of its energy needs from glucose oxidation (44). In SGA infants, there is a strong association between hypoglycemia and small head circumference measured at 12 months, 18 months, and 5 years corrected age (8). It is known that glial proliferation takes place during the third trimester of fetal life and continues after birth (80). Hypoglycemia delays astrocyte proliferation in preterm infants and up until about 4–5 weeks of age the sensorimotor cortex, thalamus, midbrain, brainstem and cerebellar vermis are the most sensitive to hypoglycemic injury besides the occipital cortex (18,19,81). Hypoglycemic brain injury is associated with a smaller head circumference and poor cognitive abilities as shown in a cohort of 249 very low birth weight infants (82). Twelve percent of these infants (30/249) had subnormal or -2 SD age adjusted head circumference values at birth, 23% (57/249) at term corrected GA, and 13% (33/249) at 8 corrected months of age. These children had lower intelligence quotient (IQ) along with lower scores for receptive language (82). In summary, the duration, severity as well as the number hypoglycemia events closely correlate with the outcome of hypoglycemia. This may manifest as early as a few hours of life in the form of seizures or coma, or may manifest later in childhood with delayed milestones, developmental delays, poor Bayley scores, motricity and perception scores, or poor test proficiency by 4th or 5th grade.

Conclusions

While we continue to strive for a precise definition of hypoglycemia, it remains one of the most common causes of morbidity in 30–60% of preterm neonates with some of them suffering serious long-term complications (75,83,84). The extent, severity, and duration of hypoglycemia is directly proportional to the poor outcomes if not treated in a timely manner. Extreme preterm infants are susceptible to multiple comorbidities due to perinatal risk factors. All these effects are exacerbated by accompanying hypoglycemia. Late preterm or near-term infants are also at similar high risk if immediate measures to prevent hypoglycemia are not put in place. Each case should be

clinically evaluated and categorized into transient or persistent hypoglycemia and all infants with persistent hypoglycemia need to be referred to a tertiary care center where advanced diagnostic and therapeutic interventions may be available. Glucose gel is a promising new tool in management of near term or late preterm neonates. A long-term neurodevelopmental follow up should be obtained for all infants who had severe and prolonged hypoglycemia and this workup should include quality neuroimaging such as MRI scans.

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Footnote

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