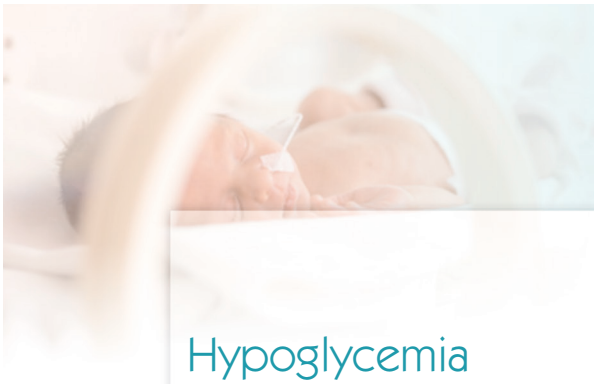

CHAPTER

28

Hypoglycemia

There is no universal definition for hypoglycemia. The "normal" range of blood glucose is variable. It depends upon factors like birth weight, gestational age, body stores, feeding status, availability of alternative energy sources (such as ketones, lactate, and free fatty acids), as well as the presence or absence of conditions that affect energy demand, such as sepsis and birth asphyxia.

DEFINITION

There is no concrete evidence to show the causation of adverse long-term outcomes by a particular level or duration of hypoglycemia. While studies have shown that persistent hyperinsulinism has a definite association with adverse neurological outcomes, there are no concrete data on the long-term adverse effects of asymptomatic hypoglycemia in at-risk neonates.[1] Hence, an "operational threshold" has been defined by consensus. It is defined as a *plasma or whole blood glucose concentration at which clinicians should consider intervention*. A blood glucose level (BGL) of less than 40 mg/dl (plasma glucose <45 mg/dl) has been taken as the operation threshold for intervention. The WHO defines hypoglycemia as a BGL of less than 45 mg/dl (2.2 mmol/L).

Blood glucose levels as low as 30 mg/dl within 1–2 hours of birth are common in normal newborns. The term "transitional neonatal hypoglycemia" (TNH) has been used to describe this transient phenomenon.[2] TNH occurs in up to 10% of normal newborns and represents a normal physiological adaptation to postnatal life.[3] The American Academy of Pediatrics (AAP) has provided guidelines for screening at-risk newborns and an algorithmic approach to management if the plasma glucose is lower than 40 mg/dl in the first 24 hours.[4]

We define hypoglycemia as a blood glucose level (BGL) of less than 40 mg/dl (plasma glucose <45 mg/dl) irrespective of age of the infant.

SCREENING FOR HYPOGLYCEMIA

Screening for hypoglycemia is recommended in following high-risk infants (Table 28.1).

In newborns considered to be at high risk of persistent hypoglycemia disorders (e.g. genetic/syndromic disorders or congenital hyperinsulinism), it is advisable to screen for hypoglycemia and also for the ability to maintain PG >70 mg/dl if one feed is missed (i.e. ability to tolerate fasting for 6–8 hours) before discharge.[6]

Schedule for Screening

There is a paucity of literature on the optimal timing and intervals of glucose monitoring. The lowest blood sugar values are seen at 2 hours of life. IDMs frequently experience asymptomatic hypoglycemia very early, viz. 1–2 hours, and rarely beyond 12 hours (range 0.8–8.5 hours), supporting the need for early screening for this population. However, preterm and SGA may be at high risk for up to 36 hours of life.

Some SGA and preterm infants may develop hypoglycemia when feeding is not established. Based on these assumptions and current

Table 28.1: Indication of routine blood glucose screening[5]

1. Birth weight <2000 g
2. Gestational age ≤35 weeks
3. Small for gestational age infants (SGA)
4. Infant of diabetic mothers (IDM)
5. Large for gestational age (LGA) infants
6. Neonates with Rh-hemolytic disease
7. Neonates born to mothers receiving therapy with terbutaline/propranolol/labetalol/oral hypoglycemic agents
8. Neonates with morphological features of growth restriction like three or more loose folds of skin around buttocks and thighs, loss of subcutaneous fat, a difference between head and chest circumference of >3 cm
9. Any sick neonate, e.g. those with perinatal asphyxia, polycythemia, sepsis, shock, etc. during the acute phase of illness
10. Family history of a genetic form of hypoglycemia
11. Congenital syndromes (e.g. Beckwith–Wiedemann), abnormal physical features (e.g. midline facial malformations, microphallus)
12. Neonates on total parenteral nutrition

Table 28.2: Schedule of blood glucose monitoring	
Category of infants	*Time schedule*
1. At-risk neonates (Table 28.1)	*2, 6, 12, 24, 48, and 72 hours of life* (72 hours for S No 3,7, and 8 in Table 28.1)
2. Sick neonates (sepsis, asphyxia, polycythemia, shock during acute phase of illness)	Every 6–8 hours (individualize as needed)
3. Neonates on parenteral nutrition	Initial 72 hours: every 6–8 hours After 72 hours: once a day

Infants exhibiting signs compatible with hypoglycemia at any time also need to be investigated

knowledge, Table 28.2 elaborates on the schedule and frequency of monitoring in different situations.

Parents should be informed that their infant is at-risk for hypoglycemia and therefore requires blood tests at regular intervals. This will ensure appropriate parental participation in monitoring and allay fears if further interventions are needed.

Infants in Whom Screening is Not Required

Screening for hypoglycemia is not recommended in healthy, breastfed, term appropriate-for-gestational age (AGA) infants. However, term infants with poor feeding, cold stress, or born to mothers with inadequate lactation may be considered for screening.

Method of Blood Glucose Level Estimation

Point-of-care (POC) reagent strips (glucose oxidase method): Though widely used, glucose estimation by this method is unreliable, especially at levels in which therapeutic intervention is required, such as BGL <40–50 mg/dl. They are useful for screening purposes, but low values must be confirmed by laboratory testing. However, treatment of hypoglycemia may be initiated based on the results of the reagent strips.

It is crucial to consider the variations between capillary and venous, blood and plasma, and immediate and stored samples (whole blood sugar value is about 15% less than that of plasma value, and the BGL can fall by 14–18 mg/dl per hour in samples that await analysis).[7] Arterial samples have slightly higher values than venous or capillary samples.

The newer generation glucose reagent strips generate a current when glucose reacts with enzymes such as glucose oxidase or

glucose dehydrogenase. The amount of current is proportional to the amount of glucose in plasma. These second-generation glucose readers are more accurate than the previous version but still unreliable in infants with low BGL. A novel approach to measuring dermal glucose concentration using highly sensitive sensors based on glucose binding protein (GBP) technology has also been developed.[8]

Recently **continuous glucose monitoring sensors** (CGMS) have been used in glucose monitoring in newborns.[9] Monitoring by CGMS helps detect hypoglycemia that may be missed on routine screening. However, many of these episodes may be clinically insignificant and thus may lead to overtreatment. Also, there are practical issues in the use of CGMS in NICU because the use of CGMS requires inserting a probe into the subcutaneous tissue, which might increase the risk of infection. Future studies are needed to determine the safety and efficacy of CGMS in the neonatal population.

Laboratory diagnosis: This is the gold standard for measuring blood glucose. Glucose can be measured by either the glucose oxidase (calorimetric) method or the glucose electrodes (used in blood gas machines). Blood samples should be analyzed quickly to avoid erroneously low glucose levels. Therefore, samples must be transported in tubes containing glycolytic inhibitors such as fluoride.

SYMPTOMS OF HYPOGLYCEMIA

It is well known that low BGL may not manifest clinically and be asymptomatic.[10] There is considerable controversy regarding the need to treat infants with low BGLs but without any symptoms.[11]

A smaller proportion of infants with hypoglycemia can be symptomatic. Symptoms of hypoglycemia include neurogenic (autonomic) and neuroglycopenic symptoms. Neurogenic symptoms occur due to sympathetic nervous discharge triggered by hypoglycemia and include both adrenergic and cholinergic responses. Neuroglycopenic symptoms result from a deficient supply of primary fuel (glucose) to the brain. Clinical signs of hypoglycemia are variable and may include stupor, jitteriness, tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, weak and high-pitched cry, lethargy, and difficulty in feeding. Episodes of sweating, sudden pallor, hypothermia, and cardiac arrest have also been reported in neonates.

DIAGNOSIS

- **Asymptomatic hypoglycemia** is said to be present when BGL is less than 40 mg/dl (to be confirmed by laboratory estimation), but the infant does not manifest any clinical features.
- **Symptomatic hypoglycemia** should be diagnosed if hypoglycemia (BGL is <40 mg/dl) coexists with clinical symptoms. Neonates generally manifest nonspecific signs that result from a variety of illnesses. Therefore, careful evaluation should be done to look for all possible causes, especially those attributed to hypoglycemia.

If clinical signs attributable to hypoglycemia persist despite intravenous glucose, then other causes of persistent/resistant hypoglycemia should be explored.

MANAGEMENT

Asymptomatic Hypoglycemia

Figure 28.1 summarizes the management of an infant with asymptomatic hypoglycemia.

Direct breastfeeding is the best option for a trial of oral feeding. If the infant cannot suck, expressed breast milk may be given. Breast milk promotes ketogenesis (ketones are important alternative sources for the brain, along with other sources such as pyruvate, free fatty acids, glycerol, and amino acids). If breast milk is not available, then formula feeds may be given.

Recently buccal dextrose gel has been used to prevent and treat asymptomatic hypoglycemia. Commercially available dextrose gel (200 mg/kg) is applied to the dried buccal mucosa, and the infant is encouraged to feed. Blood glucose is rechecked 30 minutes after gel administration. It has been found to reduce the number of episodes of hypoglycemia, recurrence rates, and need for admission to NICU and to improve exclusive breastfeeding rates at discharge in at-risk late preterm and term neonates.[12]

A few randomized clinical trials in SGA[13] and large-for-gestational age[14] infants found that the sugar or sucrose-fortified milk (5 g sugar per 100 ml milk) raises blood glucose and prevents hypoglycemia. Such supplementation may be tried in asymptomatic neonates with blood sugar levels between 20 and 40 mg/dl. However, this practice can compromise breastfeeding rates, so one should be prudent in exercising this option.

Symptomatic Hypoglycemia

All symptomatic infants should be treated with IV fluids. A 2 ml/kg bolus of 10% dextrose (200 mg/kg) should be given for symptomatic hypoglycemia (including seizures). The bolus should be followed by continuous glucose infusion at 6–8 mg/kg/min. BGL should be checked after 30 min and then every 6 hours until blood sugar is >50 mg/dl (Fig. 28.1). If BGL stays below 50 mg/dl despite bolus and glucose infusion, glucose infusion rate (GIR) should be increased in steps of 2 mg/kg/min every 15–30 min until a maximum of 12 mg/kg/min.

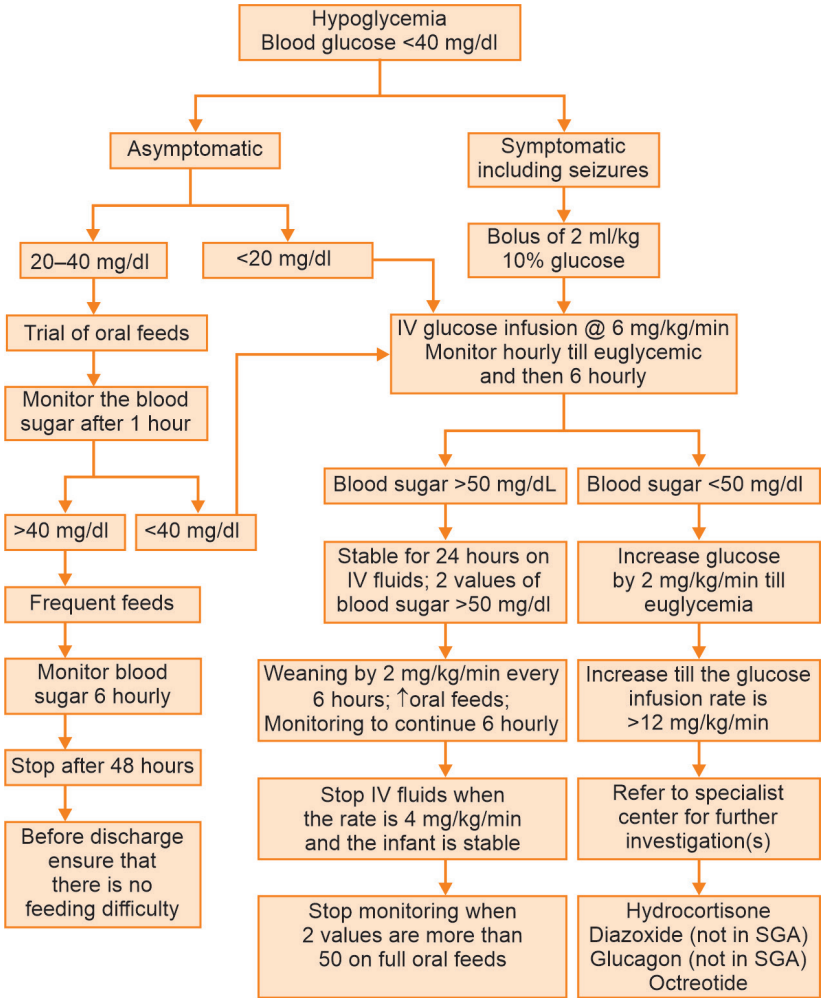

Fig. 28.1: Algorithm for management of neonatal hypoglycemia

After 24 hours of IV glucose therapy, once two or more consecutive BGLs are >50 mg/dl, the infusion can be tapered off at 2 mg/kg/min every 6 hours with BGL monitoring. A concomitant increase in oral feeds must accompany tapering. Once a rate of 4 mg/kg/min of glucose infusion and adequate oral intake is achieved, and the BGLs are consistently above 50 mg/dl, the infusion can be stopped.

It is vital to ensure continuous glucose infusion, preferably using an infusion pump without interruption. Do not stop glucose infusion abruptly, as severe rebound hypoglycemia may occur. Avoid using more than 12.5% dextrose infusion through a peripheral vein due to the risk of thrombophlebitis.

Practical tip

If there is persistent hypoglycemia, check the intravenous line for patency. Also, recheck the intravenous fluid preparation and infusion rate.

Recurrent/resistant Hypoglycemia

This condition should be considered when the infant fails to maintain normal BGL despite a GIR of 12 mg/kg/min or when stabilization is not achieved by 7 days of therapy. High levels of glucose infusion may be needed in these infants to achieve euglycemia. Hyperinsulinism must be excluded because it is the most common cause of persistent hypoglycemia. Hyperinsulinemic hypoglycemia can be congenital (due to mutations affecting the regulation of insulin secretion from the pancreas) or acquired (neonates with maternal diabetes, birth asphyxia, polycythemia, Rh incompatibility, and severe intrauterine growth restriction, Beckwith–Wiedemann syndrome, etc.). Diagnosis of hyperinsulinism is based on critical sample assay, and the criteria are given below in Table 28.3. Typical critical sample assay should include (i) glucose, (ii) insulin, (iii) cortisol, and (iv) beta-hydroxybutyrate and free fatty acids.

Other important causes of resistant hypoglycemia are listed in Table 28.4.

Besides increasing GIR, a few drugs may also be tried for resistant hypoglycemia. Before administration of drugs, take the samples to investigate the cause (Table 28.5).

The drugs that are used are listed in Table 28.6.

Do not use diazoxide or glucagon in small-for-gestational age infants.

Other management options in resistant hypoglycemia are:

1. **Mammalian target of rapamycin (mTOR) inhibitors like sirolimus, everolimus:**[16] Usually given orally in

Table 28.3: Criteria for diagnosis of hyperinsulinism
Critical sample must be drawn at time of hypoglycemia (blood glucose <40 mg/dl)
1. Detectable insulin (>2 mIU/L); usual levels with hyperinsulinism are >5–10 mIU/L.
2. Low free fatty acids (<1.5 mmol/L).
3. Low ketones (plasma β hydroxybutyrate <2.0 mmol/L).
4. Inappropriate glycemic response to 0.1 mg/kg intravenous glucagon at the time of hypoglycemia (normally glucose rise >30 mg/dl in 20 minutes).

Table 28.4: Important causes of resistant hypoglycemia[15]
A. Hyperinsulinemic hypoglycemia:
K_{ATP} channel defects
Glutamate dehydrogenase (GLUD1) activating mutation
Glucokinase activating mutation
Short-chain 3-hydroxy acyl coA dehydrogenase (SCHAD) mutation
Beckwith–Wiedemann syndrome (BWS)
B. Normoinsulinemic hypoglycemia:
Counterregulatory hormone deficiency
Cortisol deficiency (central or adrenal, e.g. hypopituitarism, congenital adrenal hyperplasia)
Growth hormone deficiency (congenital hypopituitarism)
Inborn errors of metabolism
Glycogen storage disease (I, III, VI)
Disorders of gluconeogenesis
Defects in fatty acid catabolism and ketogenesis
Organic acidurias
Galactosemia
Hereditary fructose intolerance

doses of 0.5 mg/m^2/day divided into 1–2 doses targeting a 5–15 ng/ml drug level. They act by inhibiting insulin production. Further trials are needed before incorporating them into routine use.

2. **Glucagon-like peptide 1 (GLP1) receptor antagonist:** Role in congenital hyperinsulinism. Further trials on safety and efficacy are required.
3. **Surgical treatment (near-total pancreatectomy):** In infants unresponsive to medical treatment. Consider 18F-fluro-L-DOPA PET before this to detect focal lesions in the pancreas.[17]

Table 28.5: Investigations to be done in resistant hypoglycemia*	
Blood	*Urine*
• Serum insulin levels, C-peptide, IGFBP3, thyroid hormones • Serum cortisol levels • Growth hormone levels Serum ammonia • Serum lactate levels, free fatty acids, blood BOHB Galactose 1 phosphate uridyl transferase levels • Tandem Mass spectroscopy (TMS) Genetic testing for mutations like SUR1 and KiR6.[2]	• Urine ketones • Urine reducing substances • Urine GCMS

**Samples should be taken at the time of hypoglycemia*

Table 28.6: Treatment options in resistant hypoglycemia				
Drug	*Dose*	*Route*	*Mode of action*	*Side effects*
Hydrocortisone	10 mg/kg/day BD	PO /IV	Reduces peripheral glucose utilization Increases gluconeogenesis Increases glucagon effect	Hyperglycemia, hypertension
*Diazoxide**	5–15 mg/kg/day TDS	PO	K channel agonist	Fluid retention, *hypertrichosis, cardiac failure*
Octreotide	5–35 mcg/kg/day TDS/QID	S/C	Somatostatin analogue inhibits insulin secretion	Cholelithiasis, transient growth impairment, tachyphylaxis
*Glucagon**	0.2 mg/kg	S/C or IM	Glycogenolysis, increased gluconeogenesis	Nausea, vomiting, skin rash, rebound hypoglycemia

**Do not use diazoxide or glucagon in small-for-gestational age infants.*

Some of the practically helpful formulae in the management of hypoglycemia are given in Table 28.7. The concentration of 10%

Table 28.7: Useful formulae

1. $\text{GIR (mg/kg/min)} = \frac{\text{\% of dextrose being infused} \times \text{rate (ml/hour)}}{\text{body weight (in kg)} \times 6} - \frac{(\text{D} \times \text{rate})}{(6 \times \text{weight})}$
2. $\text{Infusion rate (mg/kg/min)} = \frac{\text{IV rate (mL/kg/day)} \times \text{\% of dextrose}}{144}$
3. Infusion rate (mg/kg/min) = Fluid rate (ml/kg/day) × 0.007 × % of dextrose infused

Table 28.8: Achieving appropriate glucose infusion rate at different daily fluid intakes

Daily fluid volume (ml/kg/day)	*Glucose infusion rate (GIR)*					
	6 mg/kg/min		*8 mg/kg/min*		*10 mg/kg/min*	
	D10	*D25*	*D10*	*D25*	*D10*	*D25*
60	42	18	24	36	5	55
75	68	7	49	26	30	45
90	90	–	74	16	55	35
105	85*	–	99	6	80	25
120	100*	–	120	–	97	18

**Add 20 ml/kg of normal saline to provide 3 mEq/kg of sodium.*

dextrose and 25% dextrose to achieve appropriate glucose infusion rate (GIR) at different daily fluid intakes are given in Table 28.8.

FOLLOW-UP AND OUTCOME

The outcome of neonatal hypoglycemia is determined by factors like duration, degree of hypoglycemia, rates of cerebral blood flow and cerebral utilization of glucose, and comorbidities. Particular attention should be paid to the neurodevelopmental outcome, overall IQ, reading ability, arithmetic proficiency, and motor performance. The infants must be assessed at one month corrected age for vision. At 3, 6, 9, 12, and 18 months of corrected age, they need to be followed up for growth, neurodevelopment, vision, and hearing loss. Vision can be assessed with the Teller acuity cards, while hearing is assessed by brainstem-evoked auditory responses. Neurodevelopment must be evaluated by the clinical psychologist using DASII/similar scales. MRI at 4–6 weeks provides a good estimate of hypoglycemic injury and should be considered in the follow-up of such infants.[18]

Hypoglycemia and neurodevelopment outcome—what is the evidence?

- A systemic review involving 18 studies concluded that there is no good correlation between hypoglycemia and neurodevelopment outcome, and further well-designed, high-quality studies are needed.[19]
- Patterns of cerebral injury and neurodevelopmental outcomes were studied in 35 neonates with symptomatic hypoglycemia without evidence of HIE, and it was seen that 94% had white matter abnormalities; on follow-up at 18 months of age, 65% had impairment in development.[20]
- The recently published 'Children with Hypoglycemia and their Later Development (CHYLD)' study that prospectively evaluated the long-term effects of neonatal hypoglycemia in 477 at-risk late preterm and term neonates reported that hypoglycemia was not associated with increased risk of combined neurosensory impairment at 4.5 years but was associated with a dose-dependent increased risk of poor executive function and visual motor function; severe, recurrent and undetected episodes of hypoglycemia increased this risk.[21]

REFERENCES

1. Adamkin DH, Polin R. Neonatal hypoglycemia: is 60 the new 40? The questions remain the same. J Perinatol. 2016;36:10–2.
2. Adamkin DH. Neonatal hypoglycemia. Semin Fetal Neonatal Med. 2017;22:36–41.
3. Stanley CA, Rozance PJ, Thornton PS, De Leon DD, Harris D, Haymond MW, et al. Re-Evaluating "Transitional Neonatal Hypoglycemia": Mechanism and Implications for Management. J Pediatr. 2015;166:1520–5.e1.
4. Committee on Fetus and Newborn. Postnatal Glucose Homeostasis in Late-Preterm and Term Infants. PEDIATRICS. 2011;127:575–9.
5. Kalhan S, Parimi P. Gluconeogenesis in the fetus and neonate. Semin Perinatol. 2000;24:94–106.
6. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015;167:238–45.
7. Cowett RM, Damico LB. Capillary (heel stick) versus venous blood sampling for determination of glucose concentration in neonate. Biol Neonate. 1992. 62–6.
8. Woo HC, Tolosa L, El-Metwally D, Viscardi RM. Glucose monitoring in neonates: need for accurate and non-invasive methods. Arch Dis Child Fetal Neonatal Ed. 2014;99:F153–7.
9. Rozance PJ, Hay WW Jr. New approaches to management of neonatal hypoglycemia. Matern Health Neonatol Perinatol. 2016 May 10;2:3.
10. Lucas A, Morley R. Outcome of neonatal hypoglycemia. Br Med J. 1999;318:194.

11. Filan PM, Inder TE, Cameron FJ, et at. Neonatal hypoglycemia and occipital cerebral injury. J Pediatr. 2006;552–5.
12. Edwards T, Liu G, Battin M, Harris DL, Hegarty JE, Weston PJ, Harding JE. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database Syst Rev. 2022 Mar 18;3:CD011027.
13. Singhal PK, Singh M, Paul VK. Prevention of hypoglycemia: A controlled evaluation of sugar fortified milk feeding in small- for- date infants. Indian Pediatr. 1992;29(11):1365–9.
14. Singhal PK, Singh M, Paul VK. A controlled study of sugar fortified milk feeding in prevention of neonatal hypoglycemia. Indian J Med Res. 1991;94:342–5.
15. Thompson-Branch A, Havranek T. Neonatal Hypoglycemia. Pediatr Rev. 2017 Apr;38(4):147–57.
16. Güemes M, Hussain K. Hyperinsulinemic Hypoglycemia. Pediatr Clin North Am. 2015;62:1017–36.
17. Eichenwald EC, Hansen AR, Martin C, Stark AR, editors. Cloherty and Stark's manual of neonatal care. Eighth edition. Philadelphia: Wolters Kluwer; 2017.
18. Duvanel CB, Fawer CL, Cotting J. Long term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational age preterm infants. J Pediatr. 1999;134(4):492–8.
19. Boluyt N, Kempen A van, Offringa M. Neurodevelopment After Neonatal Hypoglycemia: A Systematic Review and Design of an Optimal Future Study. Pediatrics. 2006 Jun 1;117(6):2231–43.
20. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics. 2008;122:65–74.
21. McKinlay CJD, Alsweiler JM, Anstice NS, Burakevych N, Chakraborty A, Chase JG, et al. Association of Neonatal Glycemia With Neurodevelopmental Outcomes at 4.5 Years. JAMA Pediatrics. 2017;171:972.