



## A Brief Review of Hyperinsulinism in Small for Gestational Age Infants

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### Introduction

Small for gestational age (SGA) neonates are classically defined as having a birth weight less than two standard deviations below the mean birth weight of specific gestational age or less than the 10th percentile of a population-specific birth weight for given gestational age.<sup>(1)</sup> SGA is a statistical definition and it is not synonymous with intrauterine growth restriction (IUGR). Fetuses with IUGR fail to reach their in utero growth potential; whereas neonates who are SGA are born less than a prespecified weight percentile regardless of the etiology.<sup>(2)</sup> According to WHO 2013 statistics globally 27% of all live births are SGA and out of all of these babies two- third are born in South East Asia. India has the largest number of SGA babies worldwide with a prevalence of 46.9 %.<sup>(3)</sup> Hypoglycemia is quite common in babies with the incidence ranging from 27-52%. In this population, 98% of hypoglycemic episodes occur in the first 24 hours.<sup>(4)</sup> This signifies that in the first two days these babies are at maximum risk of hypoglycemia. The most common etiology for hypoglycemia in

this subgroup is suboptimal glycogen and fat stores, delayed appearance of Gluconeogenic enzymes and Hyperinsulinism. The incidence of Hyperinsulinism in SGA babies varies from 10-94%<sup>(4-7)</sup>.

### Diagnosis of Hyperinsulinism

Since up to one-third of SGA babies might have Hyperinsulinism hence require specific therapy so one should be aware of certain clues which point towards the hyperinsulinemic state. These clues are severe and persistent hypoglycemia within 4 to 5 hours of fasting, symptomatic hypoglycemia (Seizures, lethargy, and apnea), the requirement of high glucose infusion rate (> 10 mg/kg/minute), an absence of ketonemia or acidosis and elevated C-peptide or proinsulin levels. Diagnostic criteria's for diagnosis of Hyperinsulinism are shown in Table 1.<sup>(8)</sup> Once the diagnosis of Hyperinsulinism is established, then next question which comes to mind of the clinician is whether it is transient or persistent. Unlike hypoglycemia, there is no clear-cut timeline beyond which one can say that it is persistent hyperinsulinemia. It

may range from 4-700 days with a median time of 3-4 months.<sup>(9)</sup> Diagnosis of transient Hyperinsulinism is retrospective. If at any time baby is off drugs and maintains blood sugar then it is labeled as transient Hyperinsulinism (TH). Babies who continued to remain on Diazoxide or other medication for maintaining blood sugars or required pancreatectomy (focal or subtotal) to treat hypoglycemia are labeled as persistent hyperinsulinemic. Apart from SGA babies TH is quite common in Infants of diabetic mothers, babies born to mothers who received Intrapartum dextrose infusion, maternal toxemia, Erythroblastosis fetalis and babies with birth asphyxia. On the other hand, persistent Hyperinsulinism is associated with various genetic defects.<sup>(10)</sup>

**Table 1:** Diagnostic Criteria for Hyperinsulinemic Hypoglycemia

Parameters	Values
Plasma Insulin	> 2 µU/mL
Plasma C-peptide	> 0.2 mmol/L
Plasma Free fatty acids	< 0.5 mmol/L
Plasma Beta-hydroxybutyrate	< 0.6 mmol/L
Glycemic response to Inj. Glucagon	≥ 30 mg/dL

## Management

Now the question come in mind is that even if the baby has transient hyperinsulinemia then why one needs treatment? Earlier there was a thought that transient hypoglycemia is generally mild and resolves on its own without any major sequel. However; studies have shown that it's not benign in nature. A retrospective study in Manchester, UK showed that abnormal neurodevelopmental outcome is common in children with transient congenital Hyperinsulinism.<sup>(9)</sup> In their study, they followed a cohort of children with CHI between ages 2.5–5 years and assessed whether they have normal or abnormal neurodevelopmental outcomes in the domains of speech and language, Vision and motor. Children were classified as having persistent congenital hyperinsulinism of infancy (P-CHI), if they had undergone surgery or remained on medical therapy, or transient congenital hyperinsulinism of infancy (T-CHI) if

medical treatment for hypoglycemia was stopped. They found that the incidence of abnormal neurodevelopment was similar in both the groups (30 vs. 47% respectively, p = 0.16). Also, the prevalence of severe abnormal neurodevelopment in speech, motor, and vision domains was similar in both the groups. In this cohort, we found that the severity of disease and early presentation of CHI <7 days following birth [5.9 (1.3; 27.8), p = 0.02] were significantly associated with abnormal neurodevelopment. Other than abnormal neurodevelopmental outcome there are issues like the need of prolonged i.v infusion, increased the time taken to achieve full feed, increased risk of sepsis and increased the duration of hospital stay. Hence; it is important to identify and treat hyperinsulinemic hypoglycemia early and aggressively in order to prevent adverse neurological outcomes and other complications.

## Drugs in Hyperinsulinism

Now a day's emphasis is on the treatment of hyperinsulinemia even if it is transient. Various drugs used in HH along with their dose and mechanism of action are given in Table 2.

## Diazoxide

Diazoxide is a KATP-channel opener and the only drug approved by the Food and Drug Administration (FDA) for long-term treatment of hyperinsulinemic hypoglycemia. It is considered as the first-line drug in the management of hyperinsulinemia. Many patients of CHI may be resistant to Diazoxide due to mutations in the two genes encoding the KATP-channel of the pancreatic beta cell (ABCC8/KCNJ11).<sup>(11)</sup> But studies have shown that almost all of SGA babies with hyperinsulinemia are negative for these mutations and respond very well to Diazoxide treatment.<sup>(12)</sup> Hypertrichosis is most common and fluid retention is the most severe side effect associated with Diazoxide. There are issues with the safety of Diazoxide in preterm babies. Recently FDA issued warning that Diazoxide may be associated with pulmonary hypertension;

however, it is transient only and improves once the drug is stopped. So; as of now Diazoxide therapy is standard of care all over the world. To avoid fluid retention Chlorthiazide can be added. In summary, Diazoxide is still the first-line and FDA approved drug in the treatment of Hyperinsulinism. It is easy to use and generally well tolerated even in very preterms. Side effects which are commonly encountered are not very severe. In addition, a causal relation between Diazoxide and severe side effects still remains doubtful as there are only very few cases reported and detailed information on the course of treatment is limited.

### **Octreotide**

In countries where Diazoxide is not available or not approved for use or in cases of Diazoxide resistance; Octreotide is used as second line drug. It binds to specific membrane receptors (SSTR1-SSTR5) and has inhibitory effects on the release of hormones like glucagon and insulin from the islet cells of pancreatic and suppresses the incretin glucagon-like-peptide 1. The dose and routes of

**Table 2:** Drugs used in Hyperinsulinism

Drug	Dose	Route	Mechanism of Action
Diazoxide	5-20 mg/kg/d; 3 doses	PO	Binds to SUR1 subunit, opens K-ATP channel
Chlorthiazide	7-10 mg/kg/d; 2 doses	PO	Synergistic response to Diazoxide
Octreotide	5–25 µg/kg/d 6–8 hourly	SC Or IV	Inhibits insulin secretion by Binding to somatostatin receptors and inducing hyperpolarization of β-cells Inhibition of voltage-dependent Ca channels
Glucagon	1–20 µg/kg/h	SC/ IV	Increases glycogenolysis and gluconeogenesis
Nifedipine	0.25–2.5 mg/kg/d;3 doses	PO	Calcium channel blocker

### **Follow up**

Currently, Diazoxide is first line drug and is the only drug approved for HI so babies with HI should be started on Diazoxide. After starting therapy, there is an improvement in blood sugar levels and gradually need of glucose infusion decreases. Generally baby is said to be Diazoxide-

responsive when (i) he maintains normal blood sugars with normal frequency and volume of feeds, (ii) able to fast adequately for age and maintain normal blood glucose levels, (iii) there is low or undetectable serum insulin concentration at the end of the fasting period and (iv) there is appropriate increase in serum fatty acids and

### **Glucagon**

Glucagon is a polypeptide hormone physiologically secreted by the alpha cells of the pancreatic islets to promote hepatic glycogenolysis and gluconeogenesis and thus directly increases blood glucose levels.<sup>(10)</sup> Initially, intravenous glucagon infusion is often used in CHI for several days to weeks to maintain stable blood glucose levels, however, its long-term use is limited due to its short half-life and the need for parenteral administration. High doses of glucagon may stimulate insulin release. Catheter obstruction, Erythema necrolyticum migrans, Insulin autoantibodies are common side effects associated with Glucagon.<sup>(15,16)</sup>

ketone bodies at the end of the fasting period. Duration of therapy is quite variable. These babies are followed up regularly along with their blood sugar and ketone bodies levels and Diazoxide is tapered accordingly. Target blood sugars are according to age-related normal values.

### **Time of sending Investigations for Hypoglycemia**

Immediately after birth, in normal newborns the mean plasma glucose concentrations drop by 25–30 mg/dl to a nadir of about 55–60 mg/dl by 1–2 hours of age; then steadily rise over the first few days of life to return to the normal range by day 3.<sup>(17)</sup> Differentiation of an infant with a persistent hypoglycemia disorder may not be possible during the period of transitional neonatal hypoglycemia, but should become feasible after the period of transitional neonatal hypoglycemia has resolved by 48 to 72 hours of life.

For this reason, the Pediatric Endocrine Society guide for hypoglycemia in neonates recommends that in the first 24–48 hours of life primary focus should be on stabilization of glucose levels; whereas, after 48 hours, neonates whose glucose values remain low or who have other risk factors should be evaluated to determine the etiology of hypoglycemia and ensure their safety prior to discharge.<sup>(18)</sup> So; we also suggest sending work up after 48 hours. If workup is diagnostic of hyperinsulinemia then therapy should be instituted.

### **Conclusion**

Hypoglycemia is quite common in SGA babies and hyperinsulinemia is commonest attributable cause for it. At first sight it is difficult to state whether hyperinsulinism is transient or persistent. Since transient hyperinsulinism is also associated with poor neurological outcome one should be very aggressive in maintaining blood sugar in these babies. Workup for hypoglycemia should be sent after 48 hours of life and if on evaluation there is hyperinsulinism then diazoxide should be started.

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### **References**

- Sharma D, Farahbakhsh N, Shastri S, Sharma P. Intrauterine growth restriction – part 2. *J Matern Fetal Neonatal Med.* 2016 Dec 16; 29(24):4037–48.
- McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth Weight in Relation to Morbidity and Mortality among Newborn Infants. *N Engl J Med.* 1999 Apr 22; 340(16):1234–8.
- Lee AC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *The Lancet Global Health.* 2013;1(1):e26-e36.
- Bhat MA, Kumar P, Bhansali A, Majumdar S, Narang A. Hypoglycemia in small for gestational age babies. *Indian J Pediatr.* 2000;67(6):423–7.
- Collins JE, Leonard JV, Teale D, Marks V, Williams DM, Kennedy CR, et al. Hyperinsulinaemic hypoglycaemia in small for dates babies. *Arch Dis Child.* 1990;65:1118-20.
- Hoe FM, Thornton PS, Wanner LA, Steinkrauss L, Simmons RA, Stanley CA. Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. *J Pediatr.* 2006;148:207-12.
- Hawdon JM, Weddell A, Aynsley-Green A, Ward Platt MP. Hormonal and metabolic response to hypoglycaemia in small for gestational age infants. *Arch Dis Child.* 1993;68:269-73.
- De León DD, Stanley CA. Determination of Insulin for the Diagnosis of Hyperinsulinemic Hypoglycemia. *Best practice & research Clinical endocrinology & metabolism.* 2013;27(6):763-769.

9. Avatapalle HB, Banerjee I, Shah S, et al. Abnormal Neurodevelopmental Outcomes are Common in Children with Transient Congenital Hyperinsulinism. *Frontiers in Endocrinology*. 2013;4:60.
10. Arnoux J-B, Verkarre V, Saint-Martin C, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. *Orphanet Journal of Rare Diseases*. 2011;6:63.
11. De Lonlay P, Fournet JC, Touati G, Groos MS, Martin D, Sevin C, et al. Heterogeneity of persistent hyperinsulinaemic hypoglycaemia. A series of 175 cases. *Eur J Pediatr*. 2002;161(1):37–48.
12. Arya VB, Flanagan SE, Kumaran A, et al. Clinical and molecular characterisation of hyperinsulinaemic hypoglycaemia in infants born small-for-gestational age. *Archives of Disease in Childhood Fetal and Neonatal Edition*. 2013;98(4):F356-F358.
13. Lamberts SW, van der Lely AJ, de Herder WW, Hofland LJ. Octreotide. *N Engl J Med*. 1996;334(4):246–54.
14. Ben-Ari J, Greenberg M, Nemet D, Edelstein E, Eliakim A. Octreotide-induced hepatitis in a child with persistent hyperinsulinemia hypoglycemia of infancy. *Journal of pediatric endocrinology & metabolism: JPEM*. 2013;26(1–2):179–82.
15. Rose SR, Chrousos G, Cornblath M, Sidbury J. Management of postoperative nesidioblastosis with zinc protamine glucagon and oral starch. *J Pediatr*. 1986;108(1):97–100.
16. Mohnike K, Blankenstein O, Pfuetzner A, Potzsch S, Schober E, Steiner S, et al. Long-term non-surgical therapy of severe persistent congenital hyperinsulinism with glucagon. *Horm Res*. 2008;70(1):59–64.
17. Cornblath M, Reisner SH. Blood Glucose in the Neonate and Its Clinical Significance. *N Engl J Med*. 1965 Aug 12;273(7):378–81.
18. 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*. 167(2):238–45.