Hypoglycemia- How Long and how Frequent to Monitor in Infants of Diabetic Mothers?

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Abstract

Background: Diabetes is a very common complication seen during pregnancy. Infants born to diabetic mothers are at a higher risk for hypoglycemia. Monitoring for hypoglycemia is necessary, but the duration and the frequency has yet to be determined. *Objective:* To estimate the magnitude of hypoglycemia among infants of diabetic mothers and to determine how long the glucose level has to be monitored for those infants. *Materials and Methods:* The retrospective study was conducted in a tertiary newborn centre from January 2016 to January 2018. The inclusion criteria included all babies above 34 weeks gestation and exclusion criteria included babies admitted in NICU, with mothers on glucose infusions during delivery, on beta blockers and on anti- epileptic drugs. Total 444 infants of diabetic mothers were recruited in the present study. Descriptive analysis like mean and standard deviation were done for quantitative variables. ANOVA (Analysis of variances) test was used to compare mean capillary blood glucose values. *Results:* Out of 444 infant studied, only four (0.9%) had hypoglycemia in the first 6 hours of life. All babies achieved normal glucose values by 12 hours of postnatal age, yet sampling continued although none of the remaining results yielded values < 40 mg/dL. *Conclusion:* Glucose screening can be discontinued for all babies if feeding has been initiated and the initial three pre-feed values are above the normal range. For babies that are small for gestational age/ growth restricted (SGA/IUGR), monitoring should be tailored according to the baby's feeding pattern and growth.

Keywords: Hypoglycemia; Diabetes.

Introduction

Diabetes is the common medical complication in pregnancy, affecting about 0.5 to 5% all pregnancies [1]. The incidence of hypoglycemia in infants of diabetic mothers, though has significantly reduced, has still be a matter of concern for neonatologists worldwide. The exact threshold at which one can truly define hypoglycemia and the period of monitoring for the same, are still debatable concepts. In most of these neonates,

hypoglycemia is transient and asymptomatic. However, if hypoglycemia is missed, the neonate may become symptomatic, thus leading to long term complications.

As proposed by the American Academy of Pediatrics (AAP), based on metabolic adaptation, the guide separated the first 24 h into two sections and the operational threshold values were determinedaccordingly for asymptomatic hypoglycemia and severe hypoglycemia. For the first 4 hours, values less than 40mg/dl and from

4-24 hours, values less than 45mg/dl were considered significant for defining hypoglycemia [2].

Monitoring is usually done in many institutions by capillary blood glucose measuring by the glucometer as the values are available immediately, when compared to the venous blood sample. Studies show that the correlation between the glucometer and laboratory values is best when value is >45mg/dl and when the value is <45mg/dl, there is just a moderate correlation [3,4]. Bedside screening is helpful, but not always accurate, and should be confirmed with laboratory glucose measurement. In developing countries like India, with more of the population under the poverty line, frequent measuring of glucose for the first 48 hours, by either method, not only causes economic strain, undue anxiety for parents and also pain for the babies.

Our study is done to assess the incidence of hypoglycemia in infants of diabetic mothers. The primary outcome is to analyze the need for frequent monitoring up to 48 hours of life. The secondary outcome is to show that different babies (AGA, SGA, LGA and IGUR) have different monitoring pattern. It is one of the few studies done in India which establishes the reduced need to monitor for hypoglycemia if the initial blood glucose values are above the baseline values.

Methodology

Study Population: This was a retrospective cohort study on inborn babies more than 34 weeks gestational age, from January 2016 to January 2018 in a neonatal unit of a medical college hospital in South India. Out of 2372 deliveries conducted 614 babies were infants of diabetic mother. The exclusion criteria included all babies admitted in NICU, with mothers on glucose infusions during delivery, on beta blockers and on anti- epileptic drugs.

Sample size was calculated using the formula, n = N*X / (X + N – 1)

$X = \{(Z_{1-\alpha/2})^{2}*pq\} \div d^{2}$

N = sampling frame = 614 babies of diabetic mother

Where $Z_{1-\alpha/2}$= 95% confidence level (1.96), p= prevalence of neonatal hypoglycemia among diabetic mother = 8%,

q= (1-p) = 92% and

d = relative precision = 20% of prevalence=1.6. Thereby giving a sample size of 395.

The study protocol was approved by the institutional review board and ethics committee. In this study setting, capillary blood glucose was monitored upto 48 hours in all babies born to diabetic mothers (gestational and overt diabetes). Demographic and clinical information was obtained from hard copies and electronic medical records.

All infants were exclusively breast-fed as per hospital policy (based on baby-friendly hospital policy). For infants delivered by cesarean section, breastfeeding was started as soon as feasible and maximum within 4 hours of delivery. Based on BFHI, 24 hours rooming in and kangaroo mother care was practiced to encourage breast feeding. New borns were separated from mother only in cases of maternal illness and until she was transferred to the ward. In these cases, formula feeds were given if mother remains unavailable beyond 4 hours. No prelacteal feeds were given

Capillary blood was collected by heel prick after proper aseptic measure for screening by reagent strips method. In case of low reading, a venous blood sample was sent for laboratory confirmation by glucose oxidase method inan auto analyzer. Blood glucose values were measuredat the age of 1 hr, 2hr, 3 hr, 6 hr then Q6H till 48 hours after delivery. The cut off, was followed as per AAP guidelines (2). Lethargy, jitteriness and seizures, tremor,apnea, poor feeding etc. were considered to be clinical signs of hypoglycemia if they were unexplained by other diagnoses and corrected with the provision of glucose.

Infants found to have hypoglycemia were clinically re-examined, given an additional breast-feed and plasma glucose reassessed after 30 min. If plasma glucose remained below 2.2 mmol/l (40 mg/dl) despite additional feeding or infants became symptomatic, they were transferred to the neonatal intensive care unit for intervention and excluded from the study population.

Data were entered in Microsoft Excel and analysis were done using SPSS 16.0 version. Descriptive analysis like mean and standard deviation were done for quantitative variables and proportions for categorical variables. ANOVA (Analysis of variances) test was used to compare mean capillary blood glucose values.

Results

After taking into consideration the inclusion and exclusion criteria, 444 babies were recruited in this study. Demography of the cohort is given

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in Table 1. Total 112 babies had complications and the details are given in table 2. Among the term babies, there were 35(8.6%) SGA, 343 (84.5%) AGA, 9 (2.2%) LGA and 19 (4.7%) IUGR babies. Among the preterms, there were 2 (5.2%) SGA, 31 (81.6%) AGA, 2 (5.3%) LGA and 3 (7.9%) IUGR babies. There were only 4 babies that had hypoglycemia, within the first 6 hours of life (0.9%). This low rate is due to the early initiation of breast feeding by the mothers. They all had asymptomatic hypoglycemia that was corrected with breast feeds supplemented with formula feeds.

Capillary glucose monitoring was done for all babies and the mean for the whole cohort for each time slot has been found to be significant with p<0.001. Similarly, the mean±SD was found to be above the normal and accepted range and significant (p<0.001), but lower in LGA and IUGR babies when compared to AGA and SGA babies. Our data showed all babies achieved normal glucose values by 12 hours of postnatal age, yet sampling continued although none of the remaining results yielded values < 40 mg/dL.

Table 1: Demographic Details of the Study Population

Characteristics	Number (N)	Percentage (%)
Sex		
Male	222	50
Female	222	50
Weight		
<2000G	1	0.2
2000-2499G	46	10.4
2500-2999G	163	36.7
3000G-3499G	178	40.1
>3500G	56	12.6
Mode of Delivery		
Normal Vaginal Delivery	276	62.2
Instrumental Delivery	21	4.7
Caesarean Delivery	147	33.1
Gestational Age		
34-36^6 Weeks	38	8.6
37-39^6 Weeks	381	85.8
>40 Weeks	25	5.6
Growth		
Small for Gestational Age	37	8.3
Approximate for Gestational Age	374	84.2
Large for Gestational Age	11	2.5
Iugr	22	5

Table 2: Complications Seen in the Study Population

Characteristics	Number (N)	Percentage (%)
Pathological jaundice	45	10.1
Weight loss> 10%	34	7.7
Antenatal pelviectasis	21	4.7
Cardiac (ASD, VSD, PDA)	7	1.5
Transient Tachypnea of Newborn	5	1.1

Table 3: Glucose Levels (Mean with Sd) in Babies According to Growth for Gestational Age at Designated Times

Time	Sga	Aga	Lga	Iugr
1St Hour	60.7(7.7)	59.4(7.7)	56.2(12.6)	57.6(7.8)
2Nd Hour	65.7(8.4)	65.1(8.3)	62.9(11.9)	63.1(8.7)
3Rd Hour	69.6(7.8)	67.4(8.5)	64.5(11.7)	65.1(6.7)
6Th Hour	71.3(8.3)	69.6(9.0)	69.9(9.2)	69.0(9.3)
12Th Hour	73.4(8.0)	71.8(9.3)	69.5(10.1)	72.9(10.0)
18Th Hour	73.9(9.4)	73.6(9.4)	70.6(6.4)	70.9(9.6)
24Th Hour	73.710.8)	74.8(9.9)	81.9(15.4)	71.5(10.8)
30Th Hour	74.6(9.0)	75.7(10.5)	80.2(9.5)	73.1(13.9)
36Th Hour	71.3(9.7)	76.5(10.7)	79.0(11.8)	73.0(12.2)
42Nd Hour	74.2(10.0)	78.6(10.7)	81.1(14.9)	72.1(12.0)
48Th Hour	74.7(10.2)	79.4(10.1)	83.5(13.8)	77.3(9.7)

The mean capillary blood glucose values in the whole cohort and also in terms and preterms, were calculated and was found that by 12th hour, most of the babies in our study had normal glucose values. This again proves that these babies were unnecessary subjected to more sampling. There was no significant
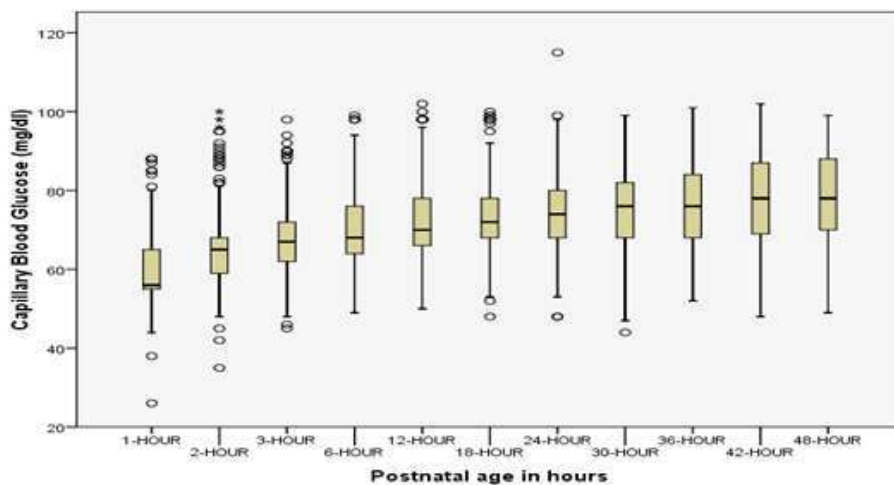

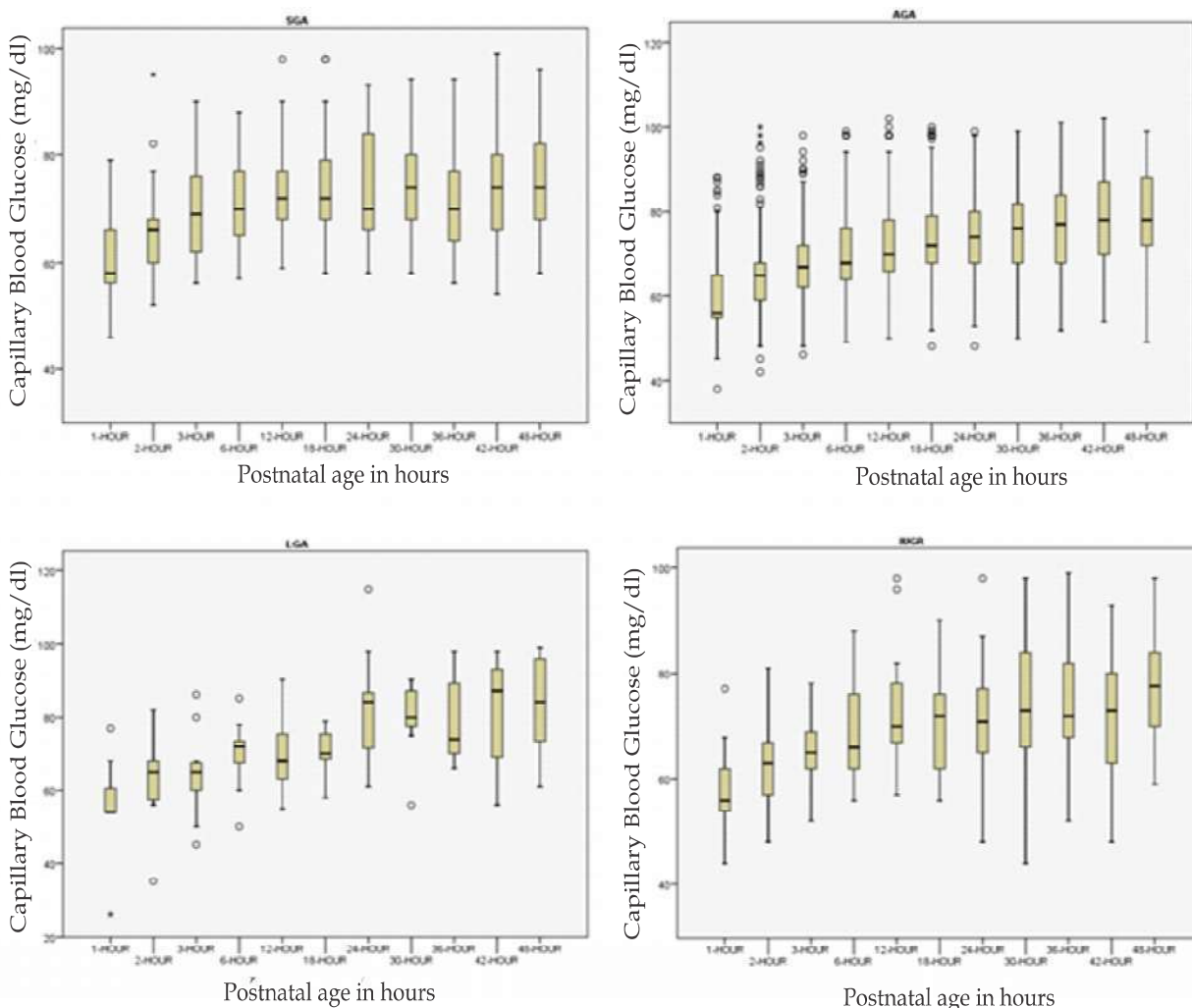**Fig. 1:** Capillary Blood Glucose Values for the Whole Cohort in the First 48 Hours of Life

Fig. 2: Capillary Blood Glucose Values for Babies According to the Growth for Gestational Age in 48 Hours
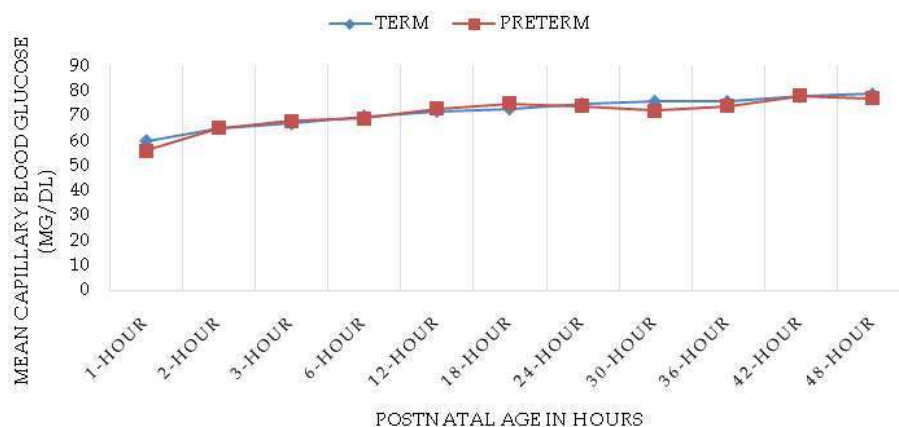
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Fig. 3: Mean Capillary Blood Glucose Values in Babies at Designated time Intervals According to Gestational Age
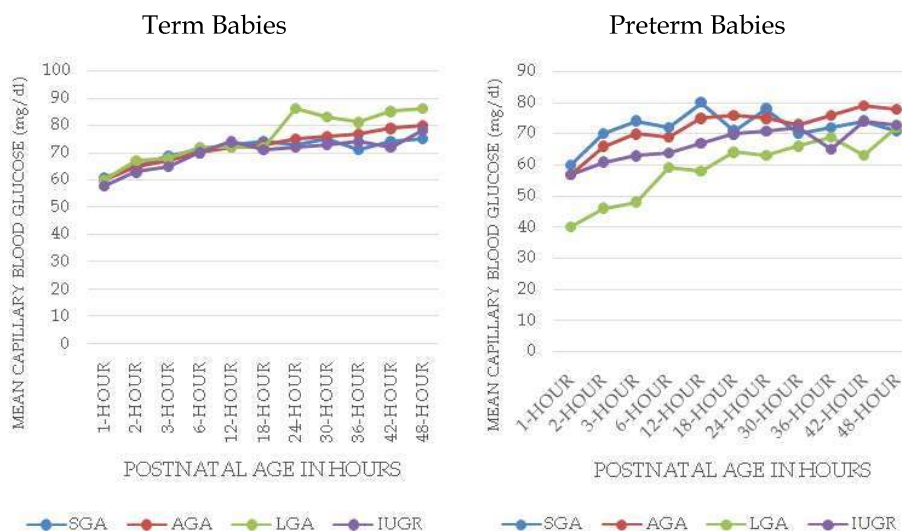

Fig. 4: Mean Capillary Blood Glucose Values in Babies at Designated Time Intervals in Term and Preterm Babies

difference in the mean glucose values in the babies based on the growth for gestational age.

Discussion

Neonatal hypoglycemia is more common in infants born to GDM mothers (30–50%) as compared to the ones born to normal mothers (0.5–4%) [5]. As stated by the Pedersen hypothesis, maternal hyperglycemia with increased placental glucose transfer to the fetus and the resultant fetal hyperinsulinemia fromfetal B-cell hyperplasia results in neonatal hypoglycemia after umbilical cord clamping [6]. In addition, decreased hepatic glucose production and diminished ability to use glycogen in the first hour of life predisposes

these infants to hypoglycemia [7]. A "metabolic" definition is the blood glucose concentration at which the counter regulatory response becomes activated.

Blood glucose determined from one sample differ whether serum, plasma, or whole blood are measured, and vary with the method of measurement [8]. Glucose reagent strips should only be considered as a screen, and if the value is low, at least one reliable laboratory plasma glucose value should be obtained to confirm the diagnosis of neonatal hypoglycemia. However, awaiting laboratory confirmation should not in a symptomatic infant [2,3,9].

There have been many studies to show that the incidence of hypoglycemia in preterm is more than

the term babies. Studies show that there was a greater incidence of hypoglycemia in preterms and the mean blood glucose values in the preterm babies were significantly lower than that of the 'term' babies [10,11]. Higher number of hypoglycemia in the preterm is probably due to very low mean birth weight in the preterm babies, immaturity of the glycogenolytic and gluconeogenesis enzymes and delayed onset of feeding. But our study showed no significant differences in terms and preterms. It could be because of the early feeding initiated, or probably due to the fact that the study included only late preterms. The third reason could be due to the less number of preterms in the study compared to the terms.

Lubchenco and Bard reported the incidences of hypoglycemia in preterm and full-term SGA neonates to be 67% and 25%, respectively, higher than those observed in AGA infants [12]. Bhat et al. showed that almost all theepisodes of hypoglycemia occurred within 24 hours in SGA babies [13]. Tenovuo A concluded a fivefold risk for hypoglycemia was seen in SGA infants [14]. Holtrop PC studied the frequency of hypoglycemia in large for gestational age infants as 8.1% and in small for gestational age infants to be 14.7% [15]. The incidence of hypoglycemia was 67% in preterm SGA group and 25% in the term SGA infants [16]. Schafer-Graf et al. reported 16% neonatal hypoglycemia rate in LGA infants [17]. Increased risk of hypoglycemia in SGA infants can be explained by decreased glycogen stores, increased insulin sensitivity and higher energy requirements.Persson et al. [18] and Leperque et al. [19] showed there were no significant differences in the risk of hypoglycemia among LGA and AGA babies of diabetic mothers, which is similar to our study results.

There is no consensus on the first blood glucose testing time. There is an immediate fall in blood glucose levels after birth because of the interruption of placental supply, reaching a nadir between 1 to 2 hours in healthy term infants [20]. The screening for hypoglycemia at first few hours of age may lead to more false-positive diagnoses and, therefore, unnecessary interventions. From 3 hours of age, blood glucose rises spontaneously, even in the absence of any feeds, due to the activation of metabolic regulatory pathways. Therefore, in the absence of abnormal clinical signs, the first blood glucose measurement is recommended after the second feed, which generally allows infants who cannot manage adequate early glucose homoeostasis to be identified [21].

There are still controversies in finalizing till when the glucose monitoring should continue for the babies born to diabetic mothers. Holtrop found that the average times for finding low glucose levels in LGA and SGA infants were 2.9 h (range 0.8 h to 8.5 h) and 6.1 h (range 0.8 h to 34.2 h), respectively [15]. Our study also shows that the LGA babies among the preterms had low glucose values in the first three hours. So screening beyond 12 hours is not required if blood glucose is maintained at 40mg/dl or higher in LGA babies. In SGA babies, if there are no feeding concerns and the infant is well, screening may be continued till 24 hours of age. After 24 hours, repeated screening before feeds should be continued if plasma glucose concentrations remain lower than 45 mg/dL. Glucose screening should continue until 12 hours of age for AGA infants born to mothers with diabetes and who maintain plasma glucose concentrations > 40 mg/dl [22].

There is currently no consensus on the frequency of glucose blood monitoring in asymptomatic infants born to diabetic mothers. Transient, single, brief periods of hypoglycemia are unlikely to cause permanent neurologic damage. Preterms and babies that LGA (above 90th percentile) or growth restricted infants (<10th percentile) born to diabetic mother may benefit from blood glucose concentration check at 3-6 hours intervals during the first day of life. On the other hand, AGA infants of diabetic mothers do not require to be monitored if the initial two glucose readings taken in the first 6 hours are normal [23].

This study was the first of its kind to be done in the South Indian population. But it has some limitations too. Firstly it is not a population based study and it represents the data of a single tertiary care hospital in South India. Secondly most of the babies in the study were term babies (91.6%). Thirdly, most of the babies were appropriate for gestational age (84.2%), very few belonged to SGA (8.3%), IUGR (5%) and LGA (2.5%). Complications of babies based on the mother's treatment (diet or insulin) were not identified.

New policies of glucose monitoring should be made and implemented after understanding this. It would be best to tailor the glucose monitoring pattern according to the babies and their clinical presentation and feeding patterns. Studies are needed to be done in a larger population with equal number of subjects at each designated time spot to know the pattern of hypoglycemia in them.

Conclusion

In conclusion, in most cases, neonatal hypoglycemia in IDM can be corrected by early feeding. In order to eliminate unnecessary sampling, institutions should review their screening practices for hypoglycemia once stable glucose levels are achieved. If inadequate postnatal glucose homeostasisis documented, the clinician must be certain that the infant can maintain normal plasma glucose values on a routine diet for a reasonably extended period (through atleast 3 feed-fast periods) before discharge.

Recommendations

- Breastfeeding should be initiated within 30 to 60 minutes of life and continued on demand.

- Feedings should be frequent; 10 to 12 times per 24 hours in the first few days after birth.

- Glucose monitoring of appropriate-for-gestational-age of term babies of non-diabetic mothers are not recommended

- Blood glucose screening of asymptomatic, at-risk infants may be initiated after two feeds, preferably 2 hours of age and every 3 h to 6 h after this, in keeping with breastfeeding practices.

- Testing may be discontinued after 12 hours in LGA and AGA babies born to diabetic mothers if blood glucose levels remain at 45mg/dl or higher.

- Testing may be continued upto 24 hours in SGA and preterm babies, It can be continued upto 36 hours in babies if feeding has not been established or blood glucose values are lower than 45mg/dl.

- Symptomatic and unwell babies require immediate glucose testing and management accordingly.

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Abbreviations

NICU: Neonatal intensive care unit

IDM: Infants of diabetic mothers

SGA: Small for gestational age

LGA: Large for gestational age

AGA: Appropriate for gestational age

IUGR: Intrauterine growth restriction

CBG: Capillary blood glucose

BFHI: Baby friendly health initiative

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