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CORD BLOOD HBA1C AND NEONATAL OUTCOMES IN INFANTS OF DIABETIC MOTHERS IN A TERTIARY CARE HOSPITAL

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Abstract

Introduction: Cord blood glycated hemoglobin (HbA1c) emerges as a promising predictive marker for identifying infants of diabetic mothers (IDMs) at high risk for neonatal complications, including hypoglycemia. This study aims to investigate the correlation between cord blood HbA1c and neonatal outcomes in IDMs, as well as to compare outcomes between babies born to overt diabetic mothers and those diagnosed with GDM during pregnancy. **Methodology:** A descriptive longitudinal study was conducted at Saveetha Medical College and Hospital, Chennai, over a 12-month period. The study included 100 babies born to diabetic mothers. Cord blood HbA1c was collected at birth, along with glucose measurements. Neonatal outcomes were assessed, including hypoglycemia, hypocalcemia, hyperbilirubinemia, and respiratory distress. Statistical analysis was performed using SPSS software. **Results:** Of the 100 babies, 30 developed hypoglycemia within the first 48 hours, with a mean HbA1c of 6.28% in hypoglycemic babies compared to 4.97% in non-hypoglycemic babies ($p<0.001$). There was a significant correlation between cord blood HbA1c and birth weight ($p=0.001$), serum bilirubin ($p<0.001$), and venous hematocrit ($p<0.001$). The ROC analysis identified a cut-off of HbA1c ≥5.7% for predicting hypoglycemia with high sensitivity (86.7%) and specificity (80%). **Discussion:** The study findings highlight the utility of cord blood HbA1c as a predictor for neonatal complications in IDMs. Higher HbA1c levels were associated with increased risk of hypoglycemia, macrosomia, and other metabolic complications. The correlation between HbA1c and birth weight, serum bilirubin, and hematocrit underscores the impact of maternal glycemic control on neonatal outcomes. **Conclusion:** Cord blood HbA1c ≥5.7% serves as a valuable indicator for identifying IDMs at risk of hypoglycemia and other metabolic complications. Early detection using this cut-off can facilitate timely interventions to improve neonatal outcomes. However, further studies are warranted to explore additional markers and optimize management strategies for IDMs.

Keywords: Cord Blood, HbA1c, Glycosylated Hemoglobin, Neonatal Outcomes, Gestational Diabetes Mellitus.

INTRODUCTION

Over the past three decades, non-communicable diseases (NCDs) have witnessed a significant surge, primarily attributed to lifestyle changes, dietary habits, and increased stress levels. Among these NCDs, diabetes has emerged as a major concern, transcending its traditional association with the elderly to affect younger populations. Of particular concern is the impact of diabetes on pregnant women, as it not only jeopardizes maternal health but also poses significant risks to fetal well-being. Gestational Diabetes Mellitus (GDM), characterized by glucose intolerance during pregnancy, has seen a notable increase in prevalence across various settings, with alarming rates reported in community-based studies. This surge in GDM prevalence raises serious concerns due to its potential implications for both maternal and neonatal outcomes, including heightened risks of morbidity and mortality. Moreover, the long-term neurodevelopmental consequences of GDM underscore the critical importance of effective management strategies. Identifying infants of diabetic mothers (IDMs) at

high risk for neonatal hypoglycemia through predictive markers like cord blood glycated hemoglobin presents a promising avenue for preventing adverse neonatal outcomes and reducing long-term complications [1].

Community-based studies have revealed a concerning trend in GDM prevalence, with rates varying across different geographic and socio-economic settings. In urban areas, GDM prevalence has soared to 17.8%, followed by 13.8% in semi-urban regions and 9.9% in rural communities. This widespread occurrence of GDM underscores the urgent need for proactive measures to mitigate its adverse effects on maternal and neonatal health.

GDM poses significant risks to both maternal and neonatal well-being, with potential consequences extending beyond the immediate perinatal period. Maternal complications associated with GDM include increased risks of hypertension, cesarean delivery, and postpartum diabetes [2]. However, perhaps the most alarming implications are observed in neonates, with GDM predisposing them to heightened risks of morbidity and mortality. Neonatal hypoglycemia, a common complication in IDMs, can lead to neurological sequelae and long-term developmental impairments if left untreated. Additionally, the increased prevalence of major congenital anomalies in infants of diabetic mothers underscores the urgent need for effective preventive strategies [3].

Cord blood glycated hemoglobin emerges as a promising predictor for identifying IDMs at high risk for neonatal hypoglycemia. By leveraging this predictive marker, healthcare providers can proactively intervene to prevent hypoglycemia and mitigate its long-term consequences. Early diagnosis and prompt management of neonatal hypoglycemia are crucial for reducing the incidence of neurological sequelae and other morbidities in IDMs [4].

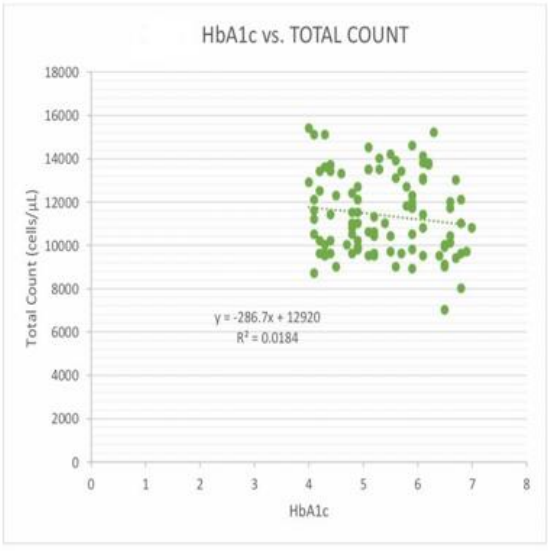

Fig: 1A

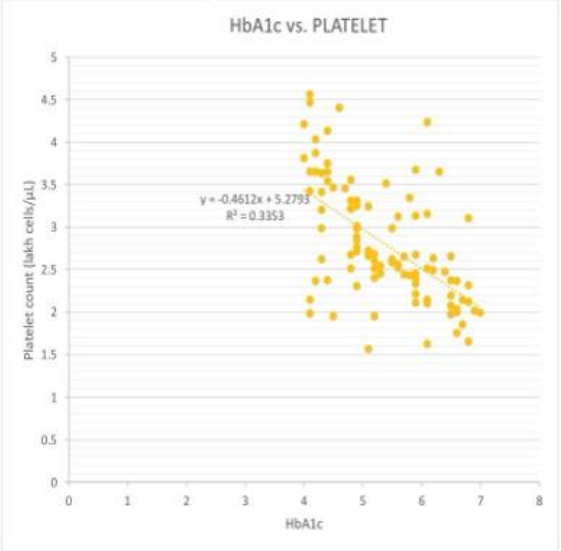

Fig: 1B

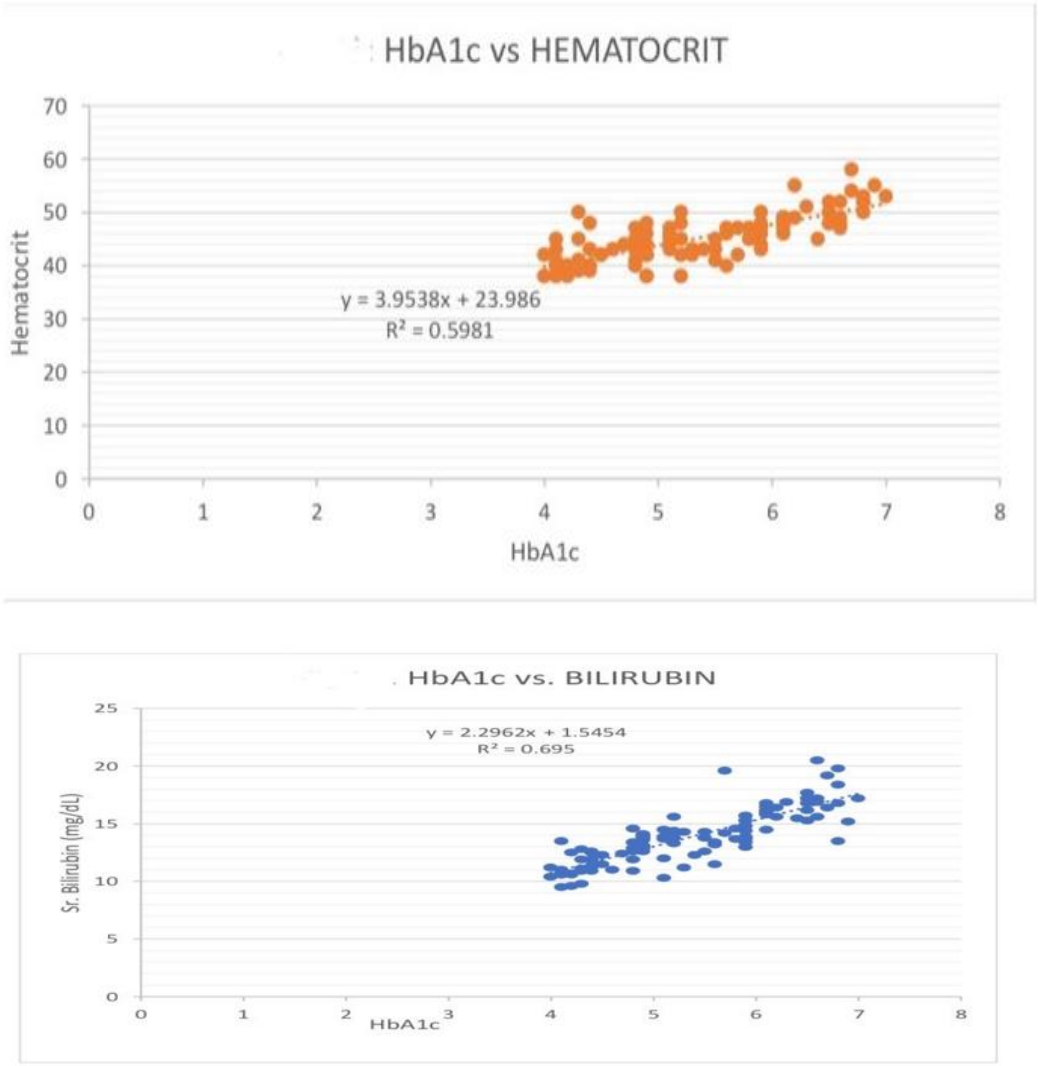

Fig: 1C

Figure 1: Correlation between HbA1c with total count, platelet, hematocrit and bilirubin

METHODOLOGY

Study design: Descriptive longitudinal study

Study setting: Institute of Child Heath, Egmore, Chennai

Study period: October 2021 – September 2022 [12 months]

Study population: 100

Inclusion criteria: All Babies born to diabetic mothers

The study was done after obtaining approval from the Institutional Ethics Committee, Madras medical college dated 15.09.2021 with IEC Reg. No: ECR/270/Inst./TN/2013/RR-20 – NO.11092021

Exclusion Criteria:

1) Early Preterm
2) IUGR
3) Birth Asphyxia
4) Meconium Aspiration Syndrome
5) Major Congenital Anomalies
6) Infants discharged before 72hrs of life
7) Risk factors for Sepsis

METHODS & PROCEDURE

The clinical details of the patients included in the study group was entered in a well-designed proforma for the study. The data was obtained by daily examination of the patients. At birth, cord blood HbA1c was collected from all babies born to diabetic mothers whether gestational or pre-gestational regardless of the type of type of therapy, i.e., meal plan, OHA, or insulin. 1ml of cord blood for HbA1c was collected in EDTA tubes. At the same time cord blood glucose was measured using glucometer. EDTA samples were stored between 2 to 8°C and processed within a week. Estimation of glycated hemoglobin was done by Nyco Card HbA1C test – Boronate affinity assay.

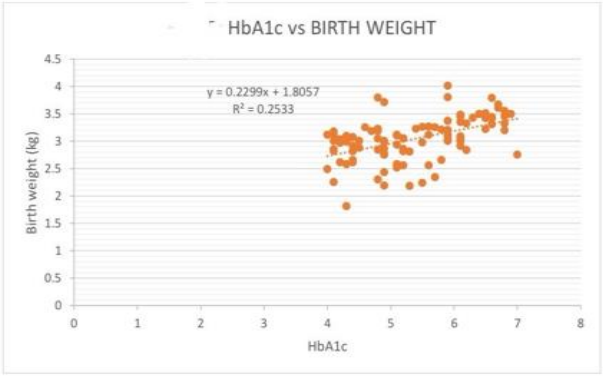

Fig: 2A

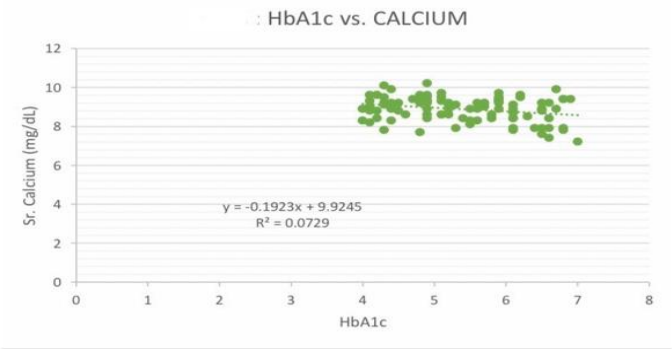

Fig: 2B

Figure 2: Correlation between HbA1c with Birth Weight and Calcium

The baby's blood glucose was monitored according to our institute protocol. Each baby was monitored for the trends of blood glucose at 2hr, 6hr, 12hr, 24hr and 48hr. Also, during the daily post-natal ward rounds, the babies were assessed for any respiratory distress, icterus and plethora. At the end of 72hrs of postnatal age, venous blood samples were collected for measuring total serum calcium, hematocrit and bilirubin levels. 1ml of blood in a plain plastic tube for serum calcium and bilirubin. Another 0.5ml of blood in EDTA tube for Complete Blood Count

Babies with confounding factors like sepsis, asphyxia, meconium aspiration, extreme preterm was excluded from the study.

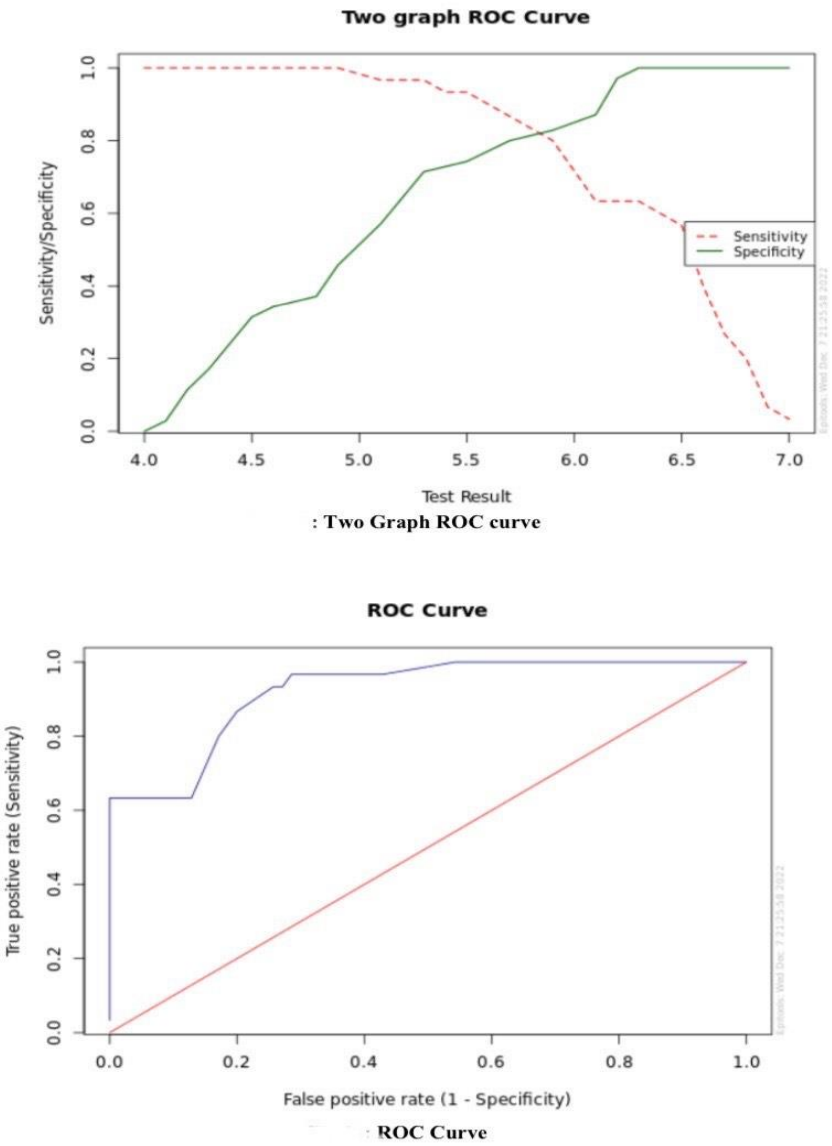

Figure 3: Two Graph ROC Curve

Statistical Analysis:

Descriptive statistical analysis was carried out in this study. Results on continuous variables is presented on mean SD (min- max) and results on categorical measurements is presented as proportions. Statistical significance is considered at a p value of 0.05. Analysis of variance (ANOVA)/ T-test was used to find the significance of study. Chi-square/Fisher exact test is used to find the significance of study parameters on categorical scale between two groups. Correlation between HbA1c and other variables is also assessed. All results are analysed using windows SPSS software.

RESULTS

The study was conducted in Saveetha medical college and hospital. A total of 100 babies born to diabetic mother were enrolled in this study.

The mean value of HbA1c among the babies were 5.36±0.87%. The mean cord blood glucose at birth was 93.79±11.11mg/dL (min = 71mg/dL; max = 120mg/dL). Of the 100 babies, 30 babies had low blood glucose in the first 48hrs of life. Of the 30 babies, 76.67% experienced hypoglycemia in the 2nd hour, while 20% and the rest 3.33% had hypoglycemia at 6th and 12th hour of life respectively. All the babies having hypoglycemia were asymptomatic.

96.6% of the 30 babies who developed hypoglycemia had HbA1c levels of more than 5%. The mean HbA1c of the hypoglycemic babies were 6.28±0.52% while those babies who didn't develop hypoglycemia had an average HbA1c of 4.97±0.67%. This data was statistically significant at $p<0.001$

It was noted that there was no difference among the term and preterm babies who developed hypoglycemia.

The rate of hypoglycemia in term infants was 28.38% while out of the 26 preterm babies 34.62%. Even though pre-term babies had a slightly higher rates of hypoglycemia when compared to term babies, it was not statistically significant. In analysis of cord blood HbA1c vs birth weight, there was direct and significant correlation between them. The $R^2=0.253$ with a $p = 0.001$ which was highly significant.

The correlation between cord blood HbA1c and serum bilirubin was highly significant at $R^2=0.695$ with $p<0.001$ [15]. The negative correlation between the HbA1c and the serum calcium was significant with p-value = 0.007. the Hypocalcemic babies had higher HbA1c which was statistically significant when compared to HbA1c of non Hypocalcemic babies. there is significant correlation between HbA1c and venous hematocrit with $P<0.001$ and $R2=0.5981$. The correlation between HbA1c and trend of Capillary Blood Glucose was studied with the heel prick blood glucose and HbA1c at 2nd, 6th, 12th, 24th and 48th hour was noted. It was evident that at 2hrs and 6hrs, the blood glucose was negatively related to HbA1c. The blood glucose at 48hrs was correlated with HbA1c but not blood glucose at 24hrs.

Of the 30 babies who developed hypoglycemia, their cord blood glucose were above 90mg/dL. Among those 30 babies, 83.3% had cord blood glucose of >100mg/dL. The average cord blood glucose was 104.8±6.4mg/dL among those who developed hypoglycemia. For non hypoglycemic IDM babies, it was 89.04± 9.21mg/dL. These values show us that when cord blood RBS was elevated (>100mg/dl), the risk of

developing hypoglycemia was significantly high with a OR=30, 95%CI: (9.31,96.71) and p<0.001.

The Cut off point for HbA1c for predicting hypoglycemia was determined using ROC curve. At HbA1c of 5.7%

Sensitivity = 0.867 (95%CI: 0.703 – 0.947)

Specificity = 0.8 (95%CI: 0.692 – 0.877)

AUC = 0.922 (95%CI: 0.869 – 0.974)

This correlates with the HbA1c cut-off obtained by ROC analysis

Positive Predictive Value = 0.65

Negative Predictive Value = 0.93

DISCUSSION

This study was undertaken to find about the correlations between the cord blood HbA1c and the outcome of the neonate in terms of metabolic complications like hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, respiratory distress, etc.

Hypoglycemia and Macrosomia:

In our analysis of the data, it was found out that out of 27 LGA babies, 20 (74.07%) of them developed hypoglycemia. Das et al [6]. in their study showed that the rate of hypoglycemia in babies weighing >4.5kg was significantly more when compared to babies born <4.5kg. In contrast, Sosensko [7] didn't find any relation between macrosomia and hypoglycemia.

HbA1c and Birth Weight:

The average HbA1c among the IDM babies, in our study, was 5.36%, with ranges from 4% to 7%. As per the figure 25 given previously, it is evident that there is significant correlation between HbA1c and birth weight of the babies with R^2=0.2533 and p=0.001.

Sosenko JM [7] did not have any correlation between cord HbA1c and birth weight Mahapatra and Raj [8] in their analysis showed cut-off of HbA1c >6.5% helped in predicting macrosomia.

HbA1c and Hypoglycemia:

Out of 100 babies, 30 babies developed hypoglycemia in the first 48hours of life. The mean HbA1c among the hypoglycemic babies were 6.28% while among the babies who did not develop hypoglycemia it was 4.9%. 23 Babies developed hypoglycemia in the 2nd hour of life. While the rest 6 and 1 baby developed hypoglycemia at 6th and 12th hour of life respectively. None of the babies who developed hypoglycemia was symptomatic.

In study conducted by Mahapatra M [8], hypoglycemia was seen in 60% of the babies and the mean HbA1c was 6.4±1%

Cord Blood Glucose and Hypoglycemia

All the IDM babies who developed hypoglycemia had their initial cord blood glucose value of >90mg/dL. The mean glucose at birth in hypoglycemic babies was 104.8±6.4mg/dL.

This was in sharp contrast to study conducted by Gupta JM and Agarwal RK [9], where the cord blood glucose in hypoglycemic babies was 62.9±18.5mg/dL

Glucose Trends

Our study shows that the lowest blood glucose was reached at 2nd hour of life and gradually increased peak at 24 hours of life. It then started to reduce slightly at 48 hours.

This was like study done by Stanley CA et al [10], where blood glucose reached lowest at 1-2hours then showed a steady increase.

HbA1c vs Hematocrit

There was a significant, yet negative, correlation between the hematocrit and HbA1c as per Fig 28 (R^2=0.5981, P<0.001).

Similar finding was also noted in a study conducted by Cetin H et al [11], which showed a significantly more hematocrit (57.65±5.73%) in IDM babies than hematocrit (47.15±1.95%) of babies born to non-diabetic mothers. This was probably due to stimulatory effect of beta-hydroxybutyrate on erythropoietic activity.

HbA1c vs Platelet

There is significant but negative correlation between HbA1c and platelet count. R=0.58; R^2=0.34; p<0.001. The study conducted by Shashikant Somani et al [12], was a case control study between diabetic and non-diabetic mothers. The platelet count of babies born to healthy mothers was 2.44±6.83 lakh cells/µL while those of IDM babies was 1.98±7.96 lakh cells/µL.

Although we did not measure the mean platelet volume (MPV) in our study, the correlation shows us that poorly controlled diabetes. The platelet count did not differ statistically between babies born to overt diabetes and babies born to mother with gestational diabetes.

HbA1c vs Serum Total Calcium

The correlation between Serum calcium and HbA1c was statistically significant, with higher HbA1c values having lesser serum calcium levels [13]. The HbA1c of Hypocalcemic babies was 6.14±0.87% when compared to non Hypocalcemic babies whose HbA1c levels were 5.25±0.84%. This was statistically highly significant.

HbA1c for predicting Hypoglycemia and Hypocalcemia

From the ROC Curve for HbA1c, the sensitivity and specificity of hypoglycemia was high. But the same cut-off applied to hypocalcemia had a low sensitivity of 76.9% and specificity of 65.5%. However, the NPV was very high with 95%.

CONCLUSIONS

This study included 100 babies born to mothers with diabetes mellitus. Among the diabetic mothers, 20% were overt diabetic, while rest 80% developed diabetes during pregnancy. 33% of the mothers took insulin for control of blood sugars, while the remaining 77% were on meal plan±OHA. The prevalence of LGA babies across all groups was 27% and they were more likely to be born out of LSCS. Across all the diabetic mothers, there was significant correlation with cord blood HbA1c vs. Birth weight/ Sr. calcium/ Hematocrit/ Platelet count/ Sr. bilirubin. The blood glucose was lowest in the babies during 2nd hour of life and gradually showed increasing trend till 24hours of life.76.6% of the 30 babies who developed hypoglycemia developed in the 2nd hour. The rate of hypoglycemia in babies was more common in overt diabetic mothers (55%) than mothers with GDM (23.75%). Similarly, cord blood HbA1c, cord blood glucose, hematocrit and bilirubin on day 3 were more in babies of overt diabetic than GDM mothers. Using a cut-off of HbA1c ≥5.7%, the sensitivity of detecting hypoglycemia was 86.7% with a specificity of 80%. At the same cut-off, however, the sensitivity and specificity of detecting hypocalcemia was low 76.9% with a specificity of 65.5%. However, the negative predictive value was very high at 95% [16]. Hence, a cord blood HbA1c cut-off of ≥5.7% could help in early identification of babies with high possibility of hypoglycemia. Also given the NPV of 95% for hypocalcemia, the possibility of hypocalcemia in IDM babies was unlikely when the HbA1c was <5.7%.

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