THE PLANET

Original Article

# Role of Cord Blood C-peptide Levels in Early Prediction of Hypoglycemia in Infants of Diabetic Mothers

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ARTICLE INFO

**Received:** 27 August 2026
**Accepted:** 30 August 2026
**Published Online:** 4 September 2026

DOI: 10.5281/zenodo.22310048

Volume: 10, Number: 2, Page: 357-362

e-ISSN: 2789-5912
ISSN: 2617-0817

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## ABSTRACT

**Background**: C-peptide measurement reflects pancreatic β-cell activity and endogenous insulin secretion. In infants of diabetic mothers, hyperinsulinemia increases glucose utilization, predisposing to early neonatal hypoglycemia. Timely identification of at-risk infants is crucial to prevent hypoglycemia-related neurological morbidity. Objective: To evaluate the role of cord blood C-peptide levels in the early prediction of hypoglycemia among infants born to diabetic mothers. **Methods & Materials**: A comparative cross-sectional study was conducted in the Department of Obstetrics and Gynecology at Dhaka Medical College Hospital. A total of 113 infants of diabetic mothers were enrolled through purposive sampling after meeting predefined inclusion and exclusion criteria. Cord blood C-peptide was measured at birth, and neonatal glucose was monitored early. Data were analyzed using SPSS 23.0 with descriptive statistics and chi-square or appropriate non-parametric tests; $p<0.05$ indicated significance at 95% confidence interval. **Results**: A significant difference was noted between hypoglycemic and normoglycemic groups ($p<0.001$). Cesarean delivery was more frequent among hypoglycemic infants (92%). Hypoglycemia predominantly occurred within 12 hours (mean glucose 2.72±0.90 mmol/L), while normoglycemic infants peaked at 6 hours (4.09±1.17 mmol/L). Maternal HbA1c and cord blood C-peptide levels were significantly higher in hypoglycemic infants ($p<0.001$). **Conclusion**: Neonatal hypoglycemia is more common in infants of diabetic mothers, particularly those delivered by cesarean section. Elevated cord blood C-peptide levels are strongly associated with hypoglycemia, indicating that C-peptide can serve as an early and reliable predictor of hypoglycemia in IDMs.

***Keywords:*** *Cesarean section, Cord blood, C-peptide, HbA1c, Hyperinsulinemia, Infant of diabetic mother, Neonatal hypoglycemia.*

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## INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Diabetes complicating pregnancy-including gestational diabetes mellitus (GDM), type 1 DM, and type 2 DM-remains a major contributor to adverse maternal, fetal, and neonatal outcomes worldwide [2]. The global burden of diabetes among women of reproductive age is increasing rapidly, with projections indicating a substantial rise in the coming decades, thereby amplifying the risk of diabetes-related pregnancy complications [3]. Infants of diabetic mothers (IDMs) are particularly susceptible to metabolic disturbances due to prolonged intrauterine exposure to maternal hyperglycemia. This exposure stimulates fetal pancreatic β-cell hyperplasia and hyperinsulinemia, a key pathophysiological mechanism underlying many neonatal complications [4]. Maternal hyperglycemia in early pregnancy is associated with spontaneous abortion and congenital anomalies, whereas exposure during the second and third trimesters primarily results in fetal hyperglycemia and compensatory hyperinsulinemia. These alterations predispose neonates to hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia, septal myocardial hypertrophy, delayed pulmonary maturation, and macrosomia after birth [5]. Neonatal hypoglycemia is one of the most frequent and clinically significant complications observed in IDMs. Following delivery, the sudden interruption of maternal glucose transfer, combined with persistent fetal hyperinsulinemia, often leads to early postnatal hypoglycemia, typically within the first few hours of life [6]. A blood glucose concentration below 2.6 mmol/L is widely accepted as the diagnostic threshold for neonatal hypoglycemia [7]. Although many IDMs experience asymptomatic hypoglycemia, unrecognized or prolonged episodes may result in seizures, brain injury, and long-term neurodevelopmental impairment [8]. Given the high metabolic demands of the neonatal brain and its limited capacity for alternative energy substrates, early identification of infants at risk is crucial. C-peptide, a 31-amino acid peptide cleaved from proinsulin, is secreted in equimolar amounts with insulin and serves as a robust marker of endogenous insulin secretion [9]. Compared with insulin, C-peptide has a longer half-life, is not affected by anti-insulin antibodies, undergoes minimal hepatic extraction, and is primarily cleared by the kidneys, making it a more reliable indicator of fetal and neonatal insulin production [10]. Consequently, cord blood C-peptide has emerged as a valuable surrogate marker of intrauterine hyperinsulinemia. Several studies have demonstrated that neonates born to diabetic mother's exhibit significantly elevated cord blood C-peptide levels, reflecting increased fetal insulin secretion in response to maternal hyperglycemia [11]. Elevated cord blood C-peptide concentrations and higher C-peptide–to–glucose ratios have been associated with poor maternal glycemic control, fetal macrosomia, and an increased risk of early neonatal hypoglycemia [12]. These findings support the concept that chronic fetal hyperinsulinemia plays a central role in the development of hypoglycemia in IDMs. Moreover, evidence suggests that higher cord blood C-peptide levels are not only linked to immediate neonatal outcomes but may also

be associated with long-term metabolic consequences, including increased adiposity and insulin resistance in childhood. This underscores the importance of optimal maternal glycemic control, particularly during the final weeks of pregnancy, to minimize fetal hyperinsulinemia and its sequelae. The present study was designed to evaluate the relationship between cord blood C-peptide levels and the risk of neonatal hypoglycemia in IDMs, as well as to assess maternal and perinatal risk factors contributing to hypoglycemia. The findings of this study add to the growing body of evidence supporting the role of cord blood C-peptide as an early predictor of hypoglycemia. Incorporating cord blood C-peptide measurement into routine neonatal risk assessment may help identify high-risk infants, allowing closer monitoring and timely intervention to prevent adverse neurological outcomes.

## METHODS & MATERIALS

This comparative cross-sectional study was conducted to evaluate the role of cord blood C-peptide levels in predicting early neonatal hypoglycemia among infants of diabetic mothers (IDMs). The study was carried out in the Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, over one year following approval of the research protocol. An ongoing review of relevant literature supported the study framework and analysis.

### Study population and sample size

The study population comprised neonates born to diabetic mothers during the study period. Sample size was calculated using the formula $n=(z^2pq)/d^2$ with a 95% confidence interval, 5% margin of error, and an assumed hypoglycemia prevalence of 8%, resulting in a sample size of 113. A total of 113 eligible neonates were enrolled using purposive sampling.

### Inclusion and exclusion criteria

Singleton, term neonates born to diabetic mothers whose guardians provided informed consent were included. Exclusion criteria were preterm birth, major congenital anomalies, severe perinatal asphyxia, twin gestation, and erythroblastosis fetalis.

### Data collection and definitions

Diabetes in pregnancy, including gestational diabetes mellitus, was diagnosed according to ADA 2020 criteria. Neonatal hypoglycemia was defined as blood glucose <2.6 mmol/L within the first 24 hours. Maternal and neonatal clinical variables were recorded using a pretested questionnaire.

### Laboratory analysis and statistical methods

Cord blood (2 mL) was collected at birth for C-peptide estimation using chemiluminescence ELISA (IMMULITE 2000, USA). Neonatal blood glucose was measured at predefined intervals up to 24 hours. Data were analyzed using SPSS version 23.0, with $p<0.05$ considered statistically significant. Ethical approval and informed consent were obtained.

## RESULTS

This study was conducted in the Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, Dhaka, from January 2022 to December 2022. A total of 113 diabetic mothers and their neonates were enrolled according to the predefined inclusion and exclusion criteria. The primary objective was to evaluate the association between cord blood C-peptide levels and neonatal hypoglycemia among infants of diabetic mothers (IDM). Regarding maternal demographic characteristics, the majority of mothers (64.6%) belonged to the 26–35 years' age group, followed by 18–25 years (20.4%) and ≥36 years (15.0%), with a mean age of 30.14 ± 4.80 years. Nearly two-fifths of the mothers were graduates (38.9%), and an equal proportion had completed higher secondary education. Most mothers were housewives (61.1%). In terms of body mass index, 63.7% were overweight, and 7.1% were obese, while only 28.3% had normal BMI.

**Table I**

Distribution of the diabetic mothers of neonates according to demographic characteristics (*n*=113).

| | Diabetic mother | n | % |
|---|---|---|---|
| Age (years) | 18-25 | 23 | 20.4 |
| | 26-35 | 73 | 64.6 |
| | ≥36 | 17 | 15.0 |
| | Mean ±SD | 30.14 ± 4.80 | |
| Educational qualification | Class 8 | 9 | 8.0 |
| | SSC | 16 | 14.2 |
| | HSC | 44 | 38.9 |
| | Graduate | 44 | 38.9 |
| Occupation | Government employee | 14 | 12.4 |
| | Non-Government employee | 27 | 23.9 |
| | Businessman | 2 | 1.8 |
| | Housewife | 69 | 61.1 |
| | others | 1 | .9 |
| Religion | Islam | 90 | 79.6 |
| | Hindu | 22 | 19.5 |
| | Christian | 1 | .9 |
| Body Mass Index | Under weight | 1 | .9 |
| | Normal | 32 | 28.3 |
| | Over weight | 72 | 63.7 |
| | Obese | 8 | 7.1 |

*Data were expressed as frequency and percentage, mean ± SD, median, and range.*

Among the neonates, 25 (22.1%) developed hypoglycemia, whereas 88 (77.9%) remained normoglycemic.

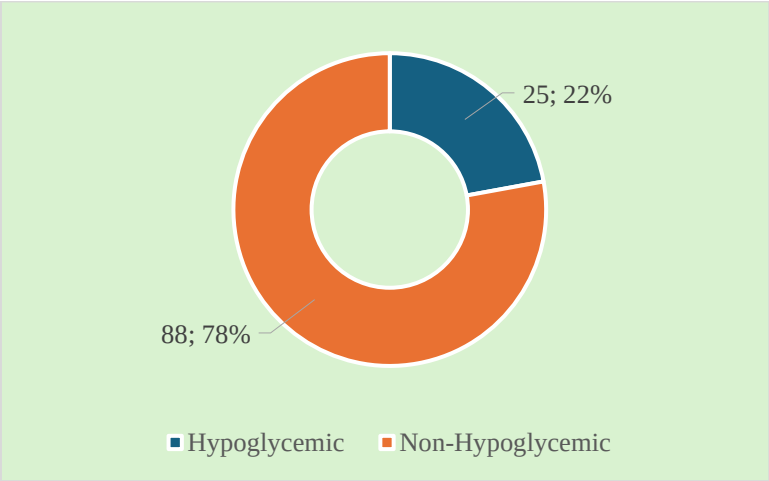


**Figure 1** Distribution of normoglycemic and hypoglycemic neonates of a diabetic mother.

Comparison of maternal characteristics between hypoglycemic and normoglycemic groups revealed no significant difference in maternal age, weight, presence of pre-eclampsia, or prolonged rupture of membranes ($p > 0.05$). However, the rate of cesarean section was significantly higher in the hypoglycemic group (92.0%) compared to the normoglycemic group (65.9%) ($p = 0.011$).

**Table II**
Comparison of maternal characteristics between normoglycemic and hypoglycemic neonates.

| Maternal characteristics | | Hypoglycemic n1=25 | Normoglycemic n2=88 | P value |
|---|---|---|---|---|
| Maternal age (years) | Mean± SD | 30.60±4.10 | 32.27±5.06 | b0.612 |
| | Median (range) | 32.0 (20.0-36.0) | 32.0 (24.0-43.0) | |
| Weight (kg) | Mean± SD | 78.84±10.04 | 75.66±13.58 | a0.832 |
| | Median (range) | 79 (70.0-90.0) | 85.5 (48.0-92.0) | |
| Pre-eclampsia | Yes | 9 (36.0) | 35 (39.8) | c0.733 |
| | No | 16 (64.0) | 53 (60.2) | |
| PROM>18 hours | Yes | 7 (28.0) | 17 (19.3) | c0.349 |
| | No | 18 (72.0) | 71 (80.7) | |
| Mode of delivery | NVD | 2 (8.0) | 30 (34.1) | c0.011 |
| | CS | 23 (92.0) | 58 (65.9) | |

*[a]Mann Whitney U test, [a] Student T test was done to determine the difference of various parameters between two groups, and [a] Chi-square test was performed to see the association between two groups. S=significant, NS= non- significant. Data were expressed as Mean± SD and Median (range), frequency, and percentage*

With respect to maternal diabetes characteristics, gestational diabetes mellitus was slightly more common in both groups, accounting for 52.0% of mothers in the hypoglycemic group and 58.6% in the normoglycemic group, though the difference was not statistically significant ($p = 0.555$). The mean duration of diabetes and the type of treatment received (diet, insulin, oral agents, or combination therapy) did not differ significantly between groups ($p > 0.05$).

**Table III**
Comparison of characteristics of normoglycemic and hypoglycemic neonates according to maternal diabetes.

| Maternal diabetes | | Hypoglycemic n1=25 | Normoglycemic n2=88 | P value |
|---|---|---|---|---|
| Type of DM | Type 2 | 12 (48.0) | 36 (41.4) | a0.555 |
| | GDM | 13 (52.0) | 51 (58.6) | |
| Duration of DM | Mean± SD | 5.07±2.28 | 4.52±2.34 | b0.413 |
| | Median (range) | 5.0 (2.0-8.0) | 5.0 (1-10.0) | |
| Treatment type of DM | Diet | 2 (8.0) | 16 (18.2) | a0.145 |
| | Insulin | 17 (68.0) | 50 (56.8) | |
| | Oral | 3 (12.0) | 3 (3.4) | |
| | Oral and Insulin | 3 (12.0) | 19 (21.6) | |

*[a] Chi-square test was performed to see the association between two groups, and [b] Mann Whitney U test was done to determine the difference in various parameters between two groups. S = significant, Data were as expressed as Mean± SD and Median (range), frequency, and percentage.*

Comparison of neonatal characteristics showed that the mean gestational age was marginally lower in the hypoglycemic group (36.6 ± 1.75 weeks) than in the normoglycemic group (37.35 ± 1.37 weeks), but this difference was not statistically significant (p = 0.09). No significant differences were observed in neonatal gender, birth weight, or APGAR scores at 1 and 5 minutes.

**Table IV**
Comparison between normoglycemic and hypoglycemic neonates according to neonatal characteristics.

| Neonatal characteristics | | Hypoglycemic n1=25 | Normoglycemic n2=88 | P value |
|---|---|---|---|---|
| Gestational age (weeks) | Mean± SD | 36.6±1.75 | 37.35±1.37 | a0.09 |
| Gender | Male | 13 (52.0) | 38 (43.2) | b0.434 |
| | Female | 12 (48.0) | 50 (56.8) | |
| Neonatal weight (kg) | Mean± SD | 3.13±0.48 | 3.22±0.74 | c0.595 |
| Apgar score1 min | Mean± SD | 8.00±0.71 | 7.79±0.59 | a0.109 |
| Apgar score 5 min | Mean± SD | 8.80±0.64 | 8.96±0.55 | a 0.217 |

*[a] Mann Whitney U test, [a] Student T test was done to determine the difference of various parameters between two groups, and [a] Chi-square test was performed to see the association between two groups.*
*S=significant, NS= non- significant, Data were expressed as Mean± SD and Median (range)*

Serial blood glucose measurements during the first 24 hours of life demonstrated significantly lower glucose levels in hypoglycemic neonates at all time points compared to normoglycemic neonates (p < 0.05). The lowest mean glucose level in the hypoglycemic group was observed at 12 hours of life (2.72 ± 0.90 mmol/L). More than half of hypoglycemic episodes (51.9%) occurred at 12 hours, followed by 3 hours (44.4%). Maternal glycemic control, assessed by HbA1c, was significantly poorer among mothers of hypoglycemic neonates (7.77 ± 0.48%) compared to those with normoglycemic neonates (7.19 ± 0.86%) (p < 0.001). Cord blood C-peptide levels were also significantly higher in hypoglycemic neonates (10.11 ± 5.65 ng/ml) than in normoglycemic neonates (3.92 ± 4.98 ng/ml) (p < 0.001), indicating a strong association between elevated C-peptide levels and neonatal hypoglycemia.

**Table V**
Comparison between normoglycemic and hypoglycemic IDM according to blood glucose during the first 24 h of life.

| Neonatal blood glucose level | | Hypoglycemic n1=25 | Normoglycemic n2=88 | P value |
|---|---|---|---|---|
| At birth | Mean± SD | 4.04±0.695 | 5.67±2.52 | <0.001 |
| | Median (range) | 4.2 (2.80-6.20) | 4.8 (2.9-16.40) | |
| 30 minutes | Mean± SD | 3.30±0.703 | 4.99±1.99 | <0.001 |
| | Median (range) | 3.8 (2.2-4.20) | 3.95 (3.20-9.80) | |
| 1 hours | Mean± SD | 3.37±0.45 | 4.49±1.86 | 0.025 |
| | Median (range) | 3.20 (2.00-4.20) | 3.7 (2.0-8.6) | |
| 3 hours | Mean± SD | 2.78±0.765 | 4.22±1.63 | <0.001 |
| | Median (range) | 2.8 (1.90-4.20) | 3.6 (2.90-9.60) | |
| 6 hours | Mean± SD | 2.86±0.781 | 4.02±1.26 | |
| | Median (range) | 3.1 (1.60-4.10) | 3.7 (2.8-8.2) | <0.001 |
| 12 hours | Mean± SD | 2.72 ±0.902 | 4.09±1.177 | |
| | Median (range) | 2.20 (1.60-4.20) | 3.9 (1.8-7.8) | <0.001 |
| 18 hours | Mean± SD | 3.04±0.87 | 4.37±1.65 | |
| | Median (range) | 3.2 (1.70-4.2) | 3.8 (2.9-9.70) | <0.001 |
| 24 hours | Mean± SD | 3.52±0.67 | 4.34±1.24 | 0.017 |
| | Median (range) | 3.6 (2.0-8.20) | 3.85 (2.90-8.20) | |

*Mann-Whitney U test was done to determine the difference in blood glucose level between groups, S=significant*
*Data were expressed as Mean± SD and Median (range).*

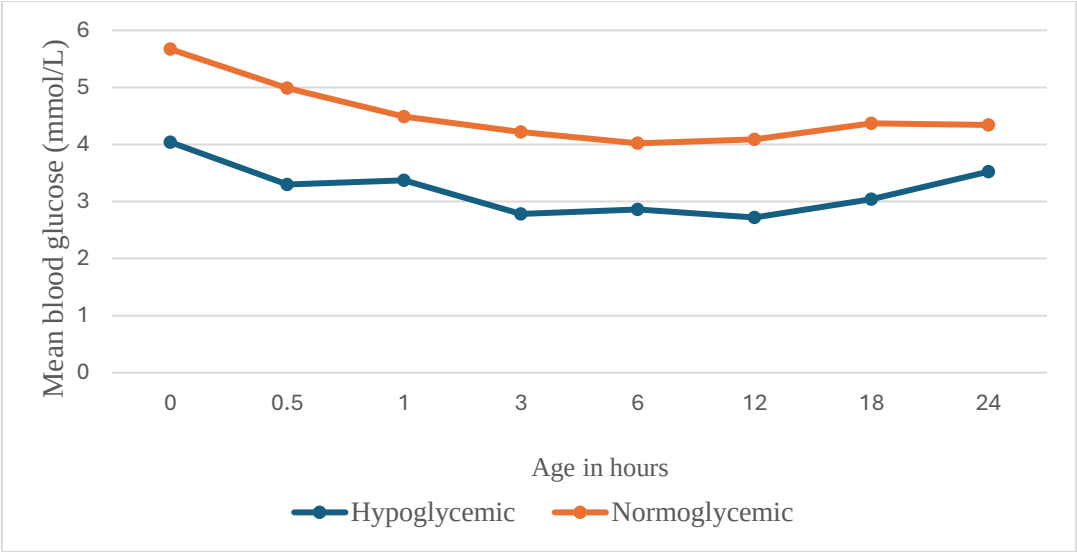


**Figure 2** Comparison between normoglycemic and hypoglycemic IDM according to blood glucose during the first 24 h of life.

**Table VI**
Comparison of HbA1c between normoglycemic and hypoglycemic IDM.

| Neonatal blood glucose level | | Hypoglycemic n1=25 | Normoglycemic n2=88 | P value |
|---|---|---|---|---|
| HbA1c | Mean± SD | 7.77±0.48 | 7.19±0.86 | <0.001 |
| | Median (range) | 7.80 (6.90-8.60) | 7.20 (5.20-9.60) | |

*The Mann-Whitney U test was performed to determine the difference in blood glucose levels between groups.*
*S=significant, Data were as expressed as Mean± SD and Median (range)*

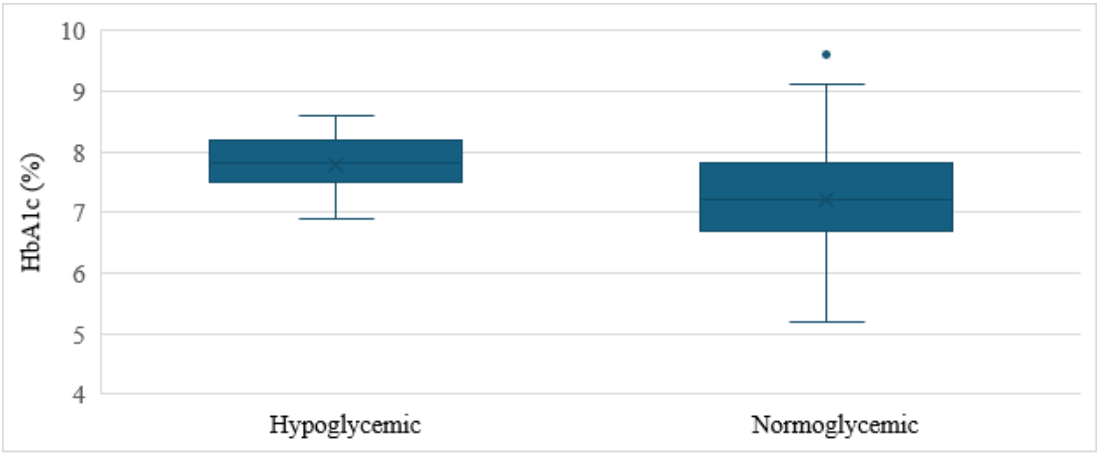


**Figure 3** Comparison between normoglycemic and hypoglycemic infants according to maternal HbA1c.

## DISCUSSION

Maintenance of glucose homeostasis is critical for neonatal survival and neurodevelopment, and hypoglycemia remains one of the most common metabolic disturbances encountered in the early neonatal period. Infants of diabetic mothers (IDMs) are particularly vulnerable due to chronic intrauterine exposure to hyperglycemia, which stimulates fetal pancreatic beta-cell hyperplasia and hyperinsulinemia. Cord blood C-peptide, secreted in equimolar amounts with insulin and less affected by hepatic metabolism, serves as a reliable marker of endogenous fetal insulin secretion and provides insight into fetal beta-cell activity [13,14]. In the present study, the majority of diabetic mothers belonged to the 26–35-year age group, with a mean age comparable to that reported in earlier studies from South Asia and other regions [15,16]. Maternal age did not differ significantly between mothers of hypoglycemic and normoglycemic neonates, a finding consistent with several previous reports indicating that maternal age alone is not a strong determinant of neonatal hypoglycemia [17,18]. Educational status and occupation were not widely discussed in earlier literature, but the predominance of housewives and graduates in this study likely reflects local sociodemographic patterns rather than disease-specific associations. Maternal overweight and obesity were common in the study population, supporting the established association between increased maternal BMI and diabetes during pregnancy [19]. However, maternal weight did not show a significant association with neonatal hypoglycemia, which aligns with earlier findings suggesting that glycemic control rather than maternal anthropometry plays a more decisive role [20]. The incidence of neonatal hypoglycemia in this study was 22.1%, which is within the wide range reported in previous studies of IDMs [21]. Variability across studies may be attributed

to differences in screening protocols, definitions of hypoglycemia, timing of glucose measurement, and maternal glycemic control. Consistent with earlier observations, most hypoglycemic episodes in this study were asymptomatic and occurred within the first 12 hours of life, emphasizing the importance of early and repeated glucose monitoring in IDMs [22]. Maternal characteristics such as pre-eclampsia and prolonged rupture of membranes were not significantly associated with neonatal hypoglycemia, findings that mirror several earlier studies. In contrast, cesarean section was significantly more frequent among hypoglycemic neonates. While causality cannot be inferred, this association may reflect higher obstetric risk, suboptimal glycemic control, or fetal distress prompting operative delivery, as reported by others [19,23]. Regarding maternal diabetes characteristics, neither the type of diabetes, duration of disease, nor treatment modality showed a significant association with neonatal hypoglycemia. These findings suggest that overall metabolic control during pregnancy, rather than diabetes subtype or treatment alone, may be more relevant to neonatal outcomes [18]. This interpretation is reinforced by the significantly higher maternal HbA1c levels observed among mothers of hypoglycemic neonates, indicating poorer glycemic control in late pregnancy. Similar associations between elevated third-trimester HbA1c and neonatal hypoglycemia have been consistently documented [21,24]. Neonatal characteristics such as gestational age, birth weight, sex, and APGAR scores did not differ significantly between hypoglycemic and normoglycemic groups. These results are consistent with previous studies reporting that hypoglycemia can occur even in term, appropriate-for-gestational-age IDMs with good immediate postnatal adaptation [22]. The most significant finding of this study is the significantly elevated cord blood C-peptide levels in hypoglycemic neonates compared to those in normoglycemic neonates. This supports the hypothesis that fetal hyperinsulinemia plays a central role in the pathogenesis of neonatal hypoglycemia in IDMs. Similar observations have been reported in multiple studies, demonstrating that elevated cord C-peptide is strongly associated with postnatal hypoglycemia and reflects poor intrauterine glycemic control [21]. These findings highlight the potential role of cord blood C-peptide as an early and objective predictor of neonatal hypoglycemia, enabling timely intervention and closer monitoring of high-risk infants.

## LIMITATIONS

A small sample size and a single-center design limited this study. Maternal glycemic control was not comprehensively assessed, C-peptide testing was costly and non-routine, and long-term follow-up of hypoglycemic infants was not performed.

## CONCLUSION

Diabetes in pregnancy, including gestational and pregestational diabetes, is associated with significant maternal and neonatal complications. Neonatal hypoglycemia remains a common problem in infants of diabetic mothers, largely due to fetal hyperinsulinemia secondary to maternal hyperglycemia. This study demonstrates a significantly higher cord blood C-peptide level among hypoglycemic neonates, indicating its value as an early predictor of hypoglycemia. The first 12 hours of life represent a critical period for glucose instability, particularly in infants delivered by cesarean section. Maternal HbA1c also emerged as an important indicator of neonatal risk.

## RECOMMENDATIONS

Larger prospective multicenter studies are recommended to validate these findings. Routine monitoring of cord blood C-peptide and early neonatal glucose levels should be considered in infants of diabetic mothers. Long-term follow-up studies are needed to assess neurodevelopmental outcomes after neonatal hypoglycemia.

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