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ORIGINAL ARTICLE

Assessment of C-Peptide in Cord Blood of Neonates of Diabetic Mothers

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ABSTRACT

Background: Understanding how C-peptide levels in the umbilical cord can be used to predict when a diabetic mother's newborn will experience hypoglycemia is urgently needed.This study aimed to assess the role of umbilical cord C-peptide levels in the early prediction of hypoglycemia among neonates of diabetic mothers.

Methods: We carried out this cross-sectional study on 52 singleton newborns born to diabetic mothersin the neonatal resuscitation room and obstetric operation room at Zagazig University Hospital. The umbilical cord C-peptide concentration was assessed via an enzyme-linked immunosorbent assay. Complete blood count, blood glucose level, insulin level, and glycated hemoglobin (HbA1C), were performed for neonates and mothers. Neonatal blood glucose was measured hourly three times.

Results: A significant association was found between neonatal C-peptide levels and maternal premature rupture of membranes (p=0.013). Compared to normoglycemic neonates, hypoglycemic neonates had significantly higher C peptide levels (p<0.001). The best cut-off value of neonatal C-peptide for the prediction of neonatal hypoglycemia is ≥0.3685 ng/ml, with an area under the curve of 0.963, a sensitivity of 88.9%, a specificity of 88.4%, a positive predictive value of 61.5%, a negative predictive value of 97.4%, and accuracy of 88.5% (p<0.001).

Conclusions: This study underscores the importance of monitoring umbilical cord C-peptide levels as a potential early predictor of neonatal hypoglycemia among infants born to diabetic mothers.

Keywords: Umbilical Cord; C-peptide; Neonate;Infants of diabetic mothers.

INTRODUCTION

Type 1 or 2 diabetes mellitus (DM) during pregnancy is associated with an increased risk of complications and death for both the mother and the newborn, even if the rate of infant mortality is currently declining at a considerable rate. Infants of diabetic mothers (IDMs) frequently experience consequences that are caused by maternallyinduced fetal hyperglycemia and hyperinsulinemia [1].

Serious birth defects, including truncus arteriosus or aortic coarctation, as well as spontaneous miscarriages, can occur if mothers have hyperglycemia in the first trimester. Pregnancy complications such as postpartum macrosomia, polycythemia, hypocalcemia, and hyperbilirubinemia, as well as delayed lung maturation, can be caused by maternal hyperglycemia in the 2nd and 3rd trimesters [2].

Asymptomatic hypoglycemia occurs in the first few hours after birth for most IDMs because the transplacental source of high glucose is interrupted after delivery. Brain damage and neurodevelopmental disorders can be accelerated by hyperinsulinemic hypoglycemia; hence, identifying and treating hypoglycemic newborns as soon as possible to prevent brain damage is crucial. Numerous publications have emphasized the value of early identification of hypoglycemic neonates [3].

Pancreatic beta cells release a 31-amino acid chain called the human C-peptide at a ratio that is equal to the insulin level. An alternative to insulin for predicting neonatal hyperinsulinemia is C-peptide, which has a longer half-life and is unaffected by certain factors involved in blood processing, such as hemolysis [4].

The risks of maternal and neonatal complications and deaths due to diabetes during pregnancy have long been recognized. Identifying and treating newborns with hypoglycemia promptly to prevent brain damage, such as hyperinsulinemia, is crucial; hypoglycemia is a leading cause of brain injury and neurodevelopmental abnormalities. Taking into account all the facets of this matter, the function of C-peptide levels in umbilical cord utilization to predict hypoglycemia early among newborns of diabetic mothers is imperative [4].

Therefore, the present study aimedto assess the role of umbilical cord C-peptide levels in the early prediction of hypoglycemia among neonates of diabetic mothers.

METHODS

We carried out this cross-sectional study on 52 children and 52 singleton newborns born to diabetic mothers at the neonatal resuscitation room and obstetric operation room, Zagazig University Hospital, for a duration of 6 months from September 2023 to February 2024. This study followed the guidelines [the World Medical Association's Code of Ethics (Declaration of Helsinki)] for human studies. All parents of the participants provided informed and written consent. The Institutional Review Board approved this research (IRB#10497).

The inclusion criterion was all singleton newborns who were born to diabetic mothers during the period of the study.

Exclusion criteria were patients who had major congenital malformations at birth resulting from any cause other than the mother’s diabetes, patients with severe perinatal asphyxia or erythroblastosis fetalis, neonates with meconium aspiration, and neonates of mothers with a history of any systemic disease such as preeclampsia or cardiac disease were excluded.

All the included children were subjected to entire history, including neonatal history events during delivery and resuscitation, antenatal history, and maternal history. The general clinical examination involved anthropometric measures,general dysmorphic features, whether the patient was cardiac or not, and assessment of vital signs.

Investigation

The umbilical cord C-peptide concentration was assessed via an enzyme-linked immunosorbent assay. complete blood count, blood glucose level, insulin level, and glycated hemoglobin (HbA1C), were performed for neonates and mothers.

Umbilical Cord (UC) serum C-peptide assessment:Blood was extracted from the umbilical cord as soon as the baby was born.

To ensure accurate glucose readings and prevent erythrocyte glycolysis, samples were collected in tubes containing sodium fluoride, held on ice until the plasma separated within one hour, and then frozen at -20 °C. The Research Institute for Endocrine Sciences' Central Laboratory collected the samples in a deep-frozen state. For every field center, the quantity of dry ice needed was determined. The shipment data were sent to the Central Laboratory. The samples were checked for frozenness upon arrival at the Central Laboratory and then stored at a temperature of -80 °C in freezer containers. The C-peptide assay did not include any samples that had hemolysis of any kind. We used an ELISA C-peptide Kit from DRG Diagnostics GmbH, an enzyme-linked immunosorbent assay, to test C-peptide.

Statistical analysis:

Data analysis was conducted via the IBM SPSS software package version 27.0 (Armonk, NY: IBM Corp), and visualization was performed via Microsoft Excel 365. Quantitative data are presented as the minimum, maximum, median, mean, interquartile range (IQR), and standard deviation (SD), whereasqualitative data are presented as numerical values and percentages (%). The Shapiro–Wilk test was performed to determine the normality of the data. Two quantitative variables with a nonnormal distribution were compared via the Mann–Whitney test, whereas more than two quantitative variables with a normal distribution were compared via one-way ANOVA. Spearman's rho test was also used to explore the relationships between two quantitative variables with no normal distribution. Furthermore, the impact strength of the independent variables was determined through multiple linear regression analysis. Statistical significance was assigned to values less than 0.05.

RESULTS

The total study sample included 52 participants, 63.5% females and 36.5% males, the gestational age revealed an average of 37.76 ± 0.962 weeks. Regarding neonatal weight, the results presented a mean weight of 3.80 ± 0.106 kilograms. Over half (53.8%) of the neonates did not exhibit any morbidity. The most prevalent morbidity was indirect hyperbilirubinemia, affecting 17.3% of the neonates. Respiratory morbidities, encompassing various respiratory conditions, were present in 9.6% of the neonates. Sepsis and polycythemia, both potentially serious conditions, were observed similarly in 3.8% of the neonates. Neonatal random blood sugar (RBS) levels yielded a mean of 73.94 ± 17.72 mg/dL in the first measurement, followed by 82.5 ± 14.6 and 89.4 ± 13.4 in the subsequent measurements. Finally, the analysis of C-peptide levels presented a mean of 0.259 ± 0.197 ng/mL, as well as a median of 0.200 and interquartile range of 0.269 (Table 1).

Parameters such as preeclampsia and PROM had prevalence rates of 26.9% and 34.6%, respectively. Cesarean section was the predominant mode of delivery (92.3%), and the duration of diabetes mellitus (DM) and type of DM treatment varied among participants (Table 2).

Neonatal C-peptide levels did not differ concerning maternal clinical parameters, but a statistically significant relationship was revealed between PROM and C-peptide levels (p=0.013) (Table 3).

Significant positive correlations were found between neonatal C-peptide and neonatal weight, duration of diabetes, and maternal HbA1c (p<0.001, <0.001, and 0.031, respectively), whilesignificant negative correlations were revealed between neonatal C-peptide levels and neonatal RBS (p<0.001) (Table 4).

Multiple linear regression analysis elucidates the impact of various clinical parameters on the concentration of neonatal C-peptide. The

regression model accounts for a modest 52.3% of the variance in C-peptide levels (R^2 = 0.523), with statistical significance (pvalue<0.001). These findings suggest that the collective predictors effectively explain the variability in C-peptide levels. The RBS of a mother has a B coefficient of 0.002, yet with a 95% confidence interval (CI) spanning from 0.002 to 0.003 and a significant p-value of <0.001, implying that it is a reliable predictor of C-peptide levels in neonates (Table 5).

A statistically significantrelationship was revealed between neonatal hypoglycemia and neonatal RBS and C peptide levels (the C peptide level was significantly lower among normoglycemic neonates, while the neonatal RBS level was significantly higher, with a p-value <0.001) (Table 6).

Statistically significant relationships were found between neonatal hypoglycemia and maternal RBS, HBA1c, and diabetes duration. The normoglycemic neonates had significantly lower maternal RBS and HBA1c and higher diabetes duration, as all were significantly greater among normoglycemic neonates, while they had significantly lower RBS (p<0.001, <0.001, and 0.001, respectively) (Table 7).

The best cut-off value of neonatal C-peptide for the prediction of neonatal hypoglycemia is ≥0.3685 ng/ml, with an area under the curve of 0.963, a sensitivity of 88.9%, a specificity of 88.4%, a positive predictive value of 61.5%, a negative predictive value of 97.4%, and accuracy of 88.5% (p<0.001) (Supplementary Table 1 and Supplementary Figure 1).

Table 1: Descriptive statistics of the demographic, clinical and neonatal parameters in the study

Parameters	Mean	Median	SD	Minimum	Maximum	IQR
Gestational age (weeks)	37.76	38.00	0.962	36.00	40.00	1.00
Neonatal weight (Kg)	3.80	3.80	0.106	3.60	4.00	0.20
Neonatal Random blood sugar (RBS) (mg/dl)	73.94	70.0	17.72	45.0	110.0	20.0
RBS 2	82.5	82.5	14.6	54.0	115.0	18.8
RBS 3	89.4	89.0	13.4	65.0	120.0	17.0
C. peptide (ng/mL)	0.259	0.200	0.197	0.061	1.109	0.269

RBS: Random blood sugar, RBS 2: Random blood sugar after 2 hours, RBS 3: Random blood sugar after 3 hours, IQR: Interquartile Range

Table 2: Maternal parameters clinical characteristics in the study

Parameters		Frequency	Percent
Preeclampsia	No	38	73.1%
	Yes	14	26.9%
PROM	No	34	65.4%
	Yes	18	34.6%
Mode of delivery	CS	48	92.3%

Parameters		Frequency	Percent
	NVD	4	7.7%
Duration of DM (years)	1	5	9.6%
	2	22	42.3%
	3	16	30.8%
	4	9	17.3%
Type of treatment of DM	Diet	7	13.5%
	Insulin	45	86.5%

PROM: premature rupture of membranes, DM: Diabetes Mellitus, CS: Cesarean Section, NVD: Normal Vaginal Delivery

Table 3: Comparison between the clinical maternal parameters regarding C. peptide, and Correlation between C peptide and the studied parameters

Parameters			C. peptide (ng/mL)	Z	p
Preeclampsia [a]	No	Median (IQR)	0.138 (0.112 – 0.358)	-0.997	0.319
	Yes	Median (IQR)	0.249(0.134 – 0.394)		
PROM [a]	No	Median (IQR)	0.134 (0.112 – 0.319)	2.488	0.013*
	Yes	Median (IQR)	0.327(0.15 – 0.434)		
Type of treatment of DM [a]	Diet	Median (IQR)	0.311 (0.112 – 0.412)	-0.972	0.331
	Insulin	Median (IQR)	0.163 (0.112 – 0.343)		
Neonatal gender [a]	Female	Median (IQR)	0.2 (0.112 – 0.408)	-1.616	0.106
	Male	Median (IQR)	0.121 (0.112 – 0.306)		

Z Man Whitney test $p<0.05$ is statistically significant
PROM: Premature Rupture of Membranes, RBS: Random Blood Sugar, HbA1c: Hemoglobin A1c, IQR: Interquartile Range

Table 4: Correlation between C peptide and the studied parameters

	r	P
Gestational age	-0.005	0.979
Neonatal weight	0.576	<0.001**
Neonatal RBS	-0.491	<0.001**
Maternal RBS	0.474	<0.001**
Maternal age	0.116	0.414
Maternal HbA1c	0.3	0.031*
Duration of diabetes	0.478	<0.001**

RBS: Random blood sugar, HbA1C: Hemoglobin A1c

Table 5: Multiple linear regression analysis for the impact of the clinical parameters on the C. peptide

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval	
	B	Std. Error	Beta	t	P	Lower	Upper
(Constant)	-0.033	0.044		-0.749	0.457	-0.121	0.055
Maternal RBS	0.002	0.000	0.723	7.403	<0.001**	0.002	0.003

**p≤0.001 is statistically highly significant

The dependent variable is neonatal C. peptide. R^2 = 0.523. (F=54.8) = 0, p-value<0.001

RBS: Random Blood Sugar, IQR: Interquartile Range

Table 6: Relation between hypoglycemia and the studied neonatal RBS and neonatal outcome:

	Normoglycemia n=43	Hypoglycemia n=9	t	p
	Mean ± SD	Mean ± SD		
Neonatal RBS (mg/dl)	78.14 ± 15.35	45.56 ± 3.01	12.795	<0.001**
	Median (IQR)	Median (IQR)	Z	p
C peptide (ng/ml)	0.14(0.11 – 0.31)	0.5(0.41 – 0.66)	-4.358	<0.001**
Neonatal weight (kg)	3.78 ± 0.09	3.92 ± 0.08	-3.84	<0.001**

t independent sample t test **p≤0.001 is statistically highly significant Z Mann Whitney test

RBS: Random Blood Sugar, IQR: Interquartile Range

Table 7: Relation between hypoglycemia and the studied maternal parameters:

	Normoglycemia N=43 (%)	Hypoglycemia N=9 (%)	χ^2	p
Preeclampsia No Yes	 30 (69.8%) 13 (30.2%)	 8 (88.9%) 1 (11.1%)	Fisher	0.415
PROM No Yes	 30 (69.8%) 13 (30.2%)	 4 (44.4%) 5 (55.6%)	Fisher	0.247
Mode of delivery: CS NVD	 40 (93%) 3 (7%)	 8 (88.9%) 1 (11.1%)	Fisher	0.544
Duration of diabetes One Two Three Four	 5 (11.6%) 20 (36.5%) 14 (32.6%) 4 (9.3%)	 0 (0%) 1 (11.1%) 3 (33.3%) 5 (55.6%)	10.266§	0.001**
Type of treatment Diet only Insulin and diet	 7 (16.3%) 36 (83.7%)	 0 (0%) 9 (100%)	Fisher	0.331
	Mean ± SD	Mean ± SD	t	p
Maternal HbA1c (%)	6.13 ± 0.88	7.74 ± 1.15	-4.374	<0.001**
Maternal RBS (mg/dl)	104.88 ± 33.44	231.11 ± 60.09	-8.84	<0.001**

t independent sample t test **p≤0.001 is statistically highly significant χ^2 Chi square test §Chi square for trend test

PROM: Premature Rupture of Membranes, CS: Cesarean Section, NVD: Normal Vaginal Delivery, HbA1c: Hemoglobin A1c, RBS: Random Blood Sugar

DISCUSSION

Diabetes mellitus (DM) during pregnancy, whether it is gestational (GDM), type 1, or type 2, continues to pose dangers to both the mother and the fetus, even though neonatal mortality has decreased significantly. Problems with maternal-induced fetal hyperglycemia and hyperinsulinemia are common in infants born to diabetic mothers [1].Severe congenital abnormalities, including truncus arteriosus or aortic coarctation, as well as spontaneous miscarriages, can result from maternal hyperglycemia in the first trimester.Most infants with gestational diabetes mellitus will have asymptomatic hypoglycemia in the first few hours after birth due to the sudden cessation of the high glucose supply of the mother. Brain injury and neurodevelopmental problems can occur in people with hyperinsulinemic hypoglycemia. Consequently, to avoid brain damage, it is crucial to detect and treat hypoglycemic neonates early. The importance of detecting hypoglycemia in neonates early has been emphasized by various studies [3].

Human C-peptide, a 31-amino acid chain released in equal amounts to insulin by pancreatic beta cells, is preferred over insulin for predicting newborn hyperinsulinemia. C-peptide is more reliable because it has a longer half-life and is unaffected by various blood processing factors, such as hemolysis [4].

We hypothesized that umbilical cord C-peptide levels could play a role in the early prediction of hypoglycemia among neonates born to diabetic mothers. To test this hypothesis, we conducted the current study to assess whether measuring C-peptide levels in the umbilical cord can effectively predict hypoglycemia in these newborns.

The current study findings regarding demographic data were similar to Asssar et al. [5] who conducted a cross-sectional study involving 50 infants born to diabetic mothers. The infants were categorized as cases if they experienced hypoglycemia within the first twenty-four hours of life and as controls if they did not. The maternal mean age was 32.4 years (± 6.15) in the case group and 34.1 years (± 6.18) in the other group, with age ranges of 20-45 and 22-41 years, respectively. The mean maternal weight was 84.7 kg (± 10.34) in the case group and 81.2 kg (± 11.31) in the second group, with weight ranges of 68-102 kg and 65-100 kg, respectively. The mean gestational age was 36.5 weeks (± 1.69) in one group and 35.4 weeks (± 2.61) in the other.

We found a significant positive correlation between HCT (%) and C. peptide. Additionally, Assar et al. [5]reported that, in the hypoglycemia group (n=31).

The present study results revealed that neonatal C-peptide levels were significantly associated with PROM (pvalue= 0.013). C-peptide level was significantly greater in the hypoglycemic group than in the normoglycemic group (p value<0.001). Similarly, a study by Assar et al. [5] reported that the mean umbilical cord C-peptide level was 5.2 ng/ml (± 0.54) among hypoglycemic patients, whereas in the normoglycemic group (n=19), it was 1.8 ng/ml (± 0.44), with a statistically significant difference (p<0.001).

The present study revealed a significant positive association between neonatal C-peptide levels and birth weight. Similarly, a study by Niknam et al. [6] demonstrated a significant association between the umbilical cord blood concentration of C-peptide and the incidence of maternal gestational diabetes mellitus and neonatal macrosomia. While the

findings of these studies are promising, there is still a lack of evidence linking C-peptide concentrations in umbilical cord blood to maternal metabolic outcomes, even though measuring C-peptide concentrations shows promise in improving the risk stratification of neonates born to overweight or diabetic mothers. Moreover, investigating molecular markers such as leptin and insulin-like growth factor-1 (IGF-1) could further enrich our understanding of the underlying mechanisms linking the umbilical cord C-peptide concentration to feto-maternal metabolic outcomes. By integrating these approaches into future research to assess the complexities of the umbilical cord C-peptide concentration and its implications for maternal and neonatal health, thus paving the way for more targeted interventions and improved clinical management strategies [7,8].

On the other hand, Andrade et al. [9] did not find a correlation between C-peptide levels and neonatal birth weight in their study of almost 6,000 pregnant women in Brazil.

The present study revealed a significant positive association between neonatal C-peptide levels and the duration of gestational diabetes. Similarly, a study by Niknam et al. [6] demonstrated a notable correlation between the concentration of C-peptide in umbilical cord blood and the gestational diabetes mellitus status of the mother.

Our study revealed no significant difference between C-peptide and maternal age. Similarly, a study by Assar et al. [5], andSaber et al. [10] revealed that maternal age was not significantly different between the hypoglycemic and normoglycemic groups. Maternal risk factors, such as preeclampsia, anemia, polyhydramnios, PROM, urinary tract infections, hypertension, and obstructed labour, also showed no significant differences between the groups. Age, weight, and the type and duration of diabetes were among the maternal demographic variables that were comparable between the hypoglycaemic and normoglycaemic groups [10].

Abo Amer et al. [11] reported that C-peptide levels in the cord were negatively correlated with blood glucose levels in the early postnatal period, suggesting that C-peptide may be associated with the risk of hypoglycemia. Begum et al. [12]reported an association between higher C-peptide levels and the risk of hypoglycemia in infants of diabetic mothers. Additionally, another study reported significant differences in haematocrit and cord C-peptide levels, with higher levels in the hypoglycaemic group, further supporting the link between these parameters and the risk of hypoglycaemia in individuals with IDM[5].

Two studies highlighted similar trends, showing that hypoglycemic infants of diabetic mothers (IDMs) had significantly higher cord C-peptide levels than normoglycemic infants did, suggesting a potential link between elevated C-peptide levels and the risk of hypoglycemia [13,14].Beta cells secrete equal amounts of C-peptide and insulin, which explains this. It is an accurate way to gauge insulin secretion, particularly after glucagon or mixed meal challenges. One of the most helpful tools for ruling out other possible causes of hyperinsulinemic hypoglycemia is C-peptide. Levels of C-peptide, an indicator of insulin synthesis, are also strongly associated with problems in newborns, such as hypoglycemia, and are directly related to the severity of diabetes in the mother [7].

The present study has several strengths: the centralization of all C-peptide measurements in a single center to minimize intra-assay variability and the meticulous adjustments

made for key confounding variables. This study addresses a significant clinical issue—neonatal hypoglycemia in infants born to diabetic mothers. The potential for using C-peptide levels as a predictive marker is directly applicable to clinical practice, offering a new tool for early diagnosis and intervention. By including various outcome measures (Birth weight, and incidence of neonatal conditions such as indirect hyperbilirubinemia and respiratory distress), this study provides a holistic view of neonatal health and the potential impact of maternal diabetes. The findings are compared with those of multiple previous studies, allowing for validation and contextualization within the broader scientific literature. This comparative approach helps identify where the study's results align with or differ from existing knowledge.

There are certain limitations in our study. The absence of specific adiposity markers, such as skin-fold thickness, total fat mass, fat-free mass, and length gain, may have limited our ability to assess neonatal body composition accurately. The lack of measurement of markers such as leptin and IGF-1 prevented a deeper exploration of potential mediators in the association between gestational weight gain and the C-peptide concentration in umbilical cord blood, as well as the reasons behind the discrepancy in the associations observed in our study compared with previous evidence.

The study included only 52 neonates, thereby reducing the applicability of the results to other contexts. You can trust the results more because they are based on data from a larger sample. This study focused on immediate postnatal outcomes without long-term follow-up to assess ongoing developmental issues or chronic conditions in infants. Longitudinal studies are necessary to understand the full impact of maternal diabetes and neonatal C-peptide levels. The study measured C-peptide levels only at birth. Measuring C-peptide levels at multiple points during pregnancy and the postpartum period could provide a more comprehensive understanding of its role in predicting neonatal outcomes. The study did not include a control group of infants born to nondiabetic mothers, which would have provided a baseline for comparing the effects of maternal diabetes on neonatal outcomes.

CONCLUSIONS

This study underscores the importance of monitoring umbilical cord C-peptide levels as a potential early predictor of neonatal hypoglycemia in infants born to diabetic mothers.Future research should explore additional factors, such as maternal BMI, gestational weight gain, and molecular markers, to elucidate the role of C-peptide in predicting adverse neonatal outcomes. By enhancing our understanding of these relationships, we can develop more effective interventions and clinical management strategies to improve the health outcomes of both mothers and their infants.

Conflict of Interest: None.

Financial Disclosure: None.

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Supplementary file

Table S1: Performance of neonatal C peptide in prediction of neonatal hypoglycemia:

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥0.3685	0.963	88.9%	88.4%	61.5%	97.4%	88.5%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant

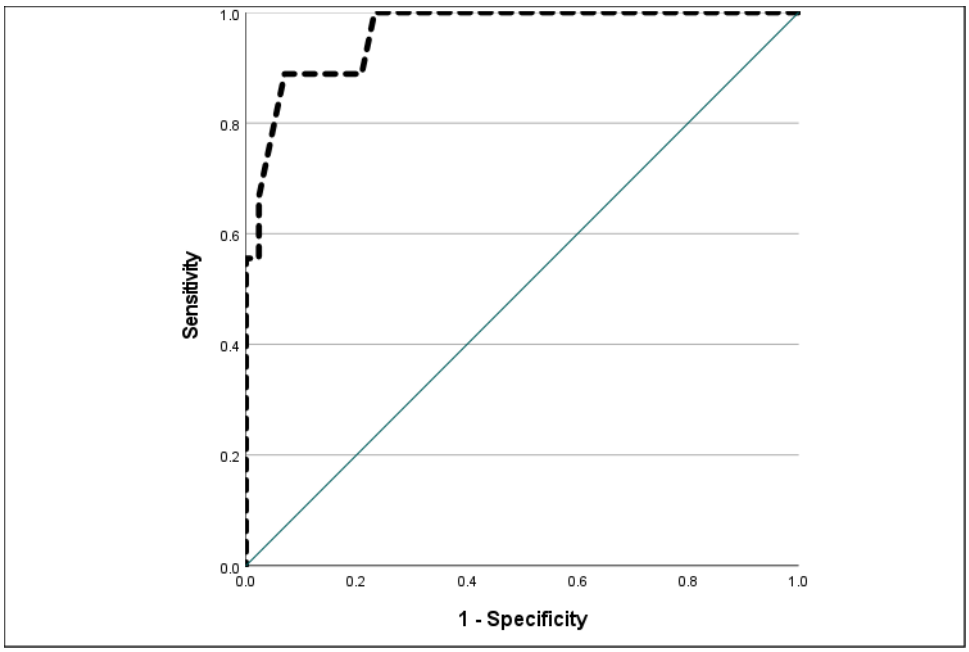

Figure S1: ROC curve showing performance of neonatal C peptide in prediction of neonatal hypoglycemia

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