Original Article

Umbilical Cord C-Peptide Level and Its Relationship to Common Early Complications in Infants of Diabetic Mothers

Ghufran Thamer Hassan, Hakim Yousif Radhi, Husam H. Hasan*

Department of Pediatrics, Babylon Health Directorate, Ministry of Health, Hillah 51001, Babylon, Iraq.

* Corresponding author: dr.husam.alshimary@gmail.com

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Abstract

Background: Diabetes during pregnancy is associated with increased maternal, fetal, and neonatal morbidity and mortality. Infants of diabetic mothers (IDM) frequently develop complications related to fetal hyperglycemia and hyperinsulinemia. Cord blood C-peptide is a reliable indicator of fetal beta-cell function due to its longer half-life and lower susceptibility to hemolysis compared with insulin. **Objectives:** To study the relationship between umbilical cord C-peptide levels and common early complications in infants of diabetic mothers. **Materials and Methods:** This cross-sectional study included 45 neonates of diabetic mothers admitted to the neonatal care unit in cooperation with the Department of Obstetrics and Gynecology, Babil Teaching Hospital, over nine months from 1 November 2022 to 31 July 2023. Cord blood C-peptide levels were measured, and serial blood glucose, serum calcium, hematocrit, and total serum bilirubin (TSB) were monitored. All neonates underwent echocardiography, abdominal and brain ultrasonography. Maternal and neonatal data were recorded. **Results:** Among 45 neonates, no significant differences were observed in maternal characteristics, including age and parity. Cord blood C-peptide levels were significantly higher in neonates with macrosomia (3.88 ± 1.11 nmol/L, $p < 0.001$), hypoglycemia at 1 hour (3.51 ± 1.17 nmol/L, $p < 0.001$), respiratory distress syndrome (RDS) (3.37 ± 1.22 nmol/L, $p = 0.005$), and hyperbilirubinemia ($p < 0.001$) compared with neonates without these complications. **Conclusion:** Elevated cord blood C-peptide levels are associated with early complications such as hypoglycemia, hyperbilirubinemia, and respiratory distress in IDMs, suggesting its potential as an early predictive marker.

Keyword: Infants of diabetic mothers, Cord blood, C-Peptide

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with disturbances in carbohydrate, fat, and protein metabolism due to impaired insulin secretion, action, or both [1]. DM in pregnancy is a common medical complication, including pregestational type 1 or type 2 diabetes and gestational diabetes mellitus (GDM) [2]. The incidence of GDM varies from 3–10%, depending on population characteristics and diagnostic criteria [3]. Several maternal factors increase the risk of GDM, including maternal age >30 years, obesity, previous GDM or macrosomic infant, family history of type 2 DM, polycystic ovary syndrome, polyhydramnios, male fetus, multiple pregnancy, non-white ethnicity, sedentary lifestyle, smoking, and psychosocial stressors such as depression [4]. Poor glycemic control during pregnancy adversely affects fetal metabolism, resulting in complications including hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia, macrosomia, and respiratory distress [5]. Infants of diabetic mothers are prone to several early complications. Hypoglycemia is most common during the first 1–4 hours after birth due to persistent fetal hyperinsulinemia and abrupt ces-

sation of maternal glucose supply [6]. Macrosomia, defined as birth weight >4 kg or >90th percentile for gestational age, results from fetal hyperinsulinemia and excess adiposity, increasing the risk of birth trauma and metabolic disorders later in life [7]. Polycythemia develops due to chronic fetal hypoxemia and hyperinsulinemia, with potential complications including thrombosis, necrotizing enterocolitis, and renal vein thrombosis [8]. Other complications include hypocalcemia, hyperbilirubinemia, RDS, prematurity, and congenital anomalies, particularly cardiac defects such as septal defects, transposition of great arteries, and hypertrophic cardiomyopathy [9]. C-peptide, a 31-amino acid peptide released equimolarly with insulin from pancreatic beta cells, has a longer half-life than insulin (20–30 minutes vs. 3–5 minutes) and is less affected during blood sampling, making it a reliable marker of fetal insulin secretion [10]. Elevated cord blood C-peptide reflects fetal hyperinsulinemia due to maternal hyperglycemia and is linked to complications including hypoglycemia, macrosomia, and RDS [11,12]. The current study aimed to investigate the relationship between cord blood C-peptide levels and early complications in infants of diabetic mothers.

Materials and Methods

Study Design and Population

This cross-sectional study included 45 term neonates of diabetic mothers admitted to the neonatal care unit at Babil Teaching Hospital between 1 November 2022 and 31 July 2023. Ethical approval was obtained from the Research Ethical Committee of the Pediatric Arab Board, Babylon Center. Written informed consent was obtained from parents.

Inclusion Criteria: All term neonates delivered to diabetic mothers during the study period.

Exclusion Criteria

Preterm neonates, those with birth asphyxia, or severe congenital malformations.

Data Collection

Maternal history (age, parity, type and management of DM) and neonatal characteristics (sex, birth weight, birth injury) were recorded. Neonates were examined for signs of hypoglycemia (jitteriness, irritability, convulsions), respiratory distress (tachypnea >60/min, grunting, accessory muscle use, oxygen requirement), and phototherapy.

Laboratory Methods

Cord blood samples (2 mL) were collected in plain tubes, centrifuged, and stored at -20°C before C-peptide assay using Human C-Peptide ELISA Kit (Cat.No E0009Hu, China). Serial blood glucose measurements were performed at 1, 2, and 4 hours. Hypoglycemia was defined as plasma glucose ≤40 mg/dL. Serum calcium, hematocrit, and total serum bilirubin were measured. Echocardiography, abdominal, and brain ultrasonography were performed in all neonates except five discharged early.

Statistical Analysis

Data were analyzed using SPSS v27. Continuous variables are expressed as mean ± SD, categorical as frequencies and percentages. Student's t-test compared continuous variables, Pearson chi-square and Fisher's exact tests assessed associations between categorical variables. ROC curve analysis evaluated sensitivity and specificity of C-peptide for predicting complications. $P \leq 0.05$ was considered significant.

Ethical approval

The study protocol was approved by the Ethical Committee of the Pediatric Arab Board, Babylon Center. Written informed consent was obtained from parents.

Results:

Maternal Characteristics

Table 1 summarizes maternal age, gravida, and parity. Most mothers were 20–40 years old (88.9%), and 77.8% were gravida 1–4. No significant demographic differences were observed.

Table 1: Distribution of diabetic mothers according to characteristics (N=45)

Mother characteristics	No.	%
Age (years)		
< 20 years	0	0.00%
20-30 years	18	40.00%
30-40 years	22	48.90%
≥ 40 years	5	11.10%
Total	45	100.00%
Gravida		
G1-G4	35	77.80%
G5-G7	10	22.20%
Total	45	100.00%
Parity		
P1-P4	41	91.20%
P5-P7	4	8.80%
Total	45	100.00%

Maternal Diabetes Type and Management

Table 2 shows 44.4% had GDM; 42.2% were treated with metformin.

Table 2: Distribution of maternal diabetes type and treatment (N=45)

Study variables		No.	%
Type of diabetes mellitus	**Type 1**	7	15.60%
	Type 2	18	40.00%
	Gestational diabetes	20	44.40%

Neonatal Characteristics

The mean birth weight was 3.61 ± 0.47 kg; 53.3% were male (Table 3).

Table 3: Neonatal characteristics (N=45)

Neonatal characteristics		Neonates of diabetic mothers (N=45)
Weight (Kg)		3.61 Kg (± 0.47 SD)
Sex	**Male**	24 (53.3)
	Female	21 (46.7)
Total		45 (100.0)

Neonatal Complications

Hypoglycemia occurred in 57.8% of neonates; hypocalcemia in 60%; polycythemia in 53.3%; RDS in 51.1% (Table 4). Mean TSB was 11.36 ± 2.81 mg/dL; 60% required phototherapy (Table 5). Macrosomia occurred in 44.4% (Figure 1). Abnormal ECHO findings were present in 75.6%, abnormal abdominal US in 20%, abnormal brain US in 2.5% (Table 6).

Table 4: Distribution of neonates of diabetic mothers according to neonatal complications

Neonatal complications	No.	%
Hypoglycemia AT 1ST HOUR (RBS ≤ 40 mg/dl)		
Present	26	57.80%
Absent	19	42.20%
Total	45	100.00%
Hypocalcemia (Serum Ca < 8.5mg/dl)		
Present	27	60.00%
Absent	18	40.00%
Total	45	100.00%
Polycythemia (PCV ≥ 65 %)		
Present	24	53.30%
Absent	21	46.70%
Total	45	100.00%
RDS		
Present	23	51.10%
Absent	22	48.90%
Total	45	100.00%

Table 5 show distribution of neonates of diabetic mothers according to total serum bilirubin level

(mg/dl) and treatment of jaundice by phototherapy. Mean TSB of total neonates of diabetic mothers was (11.36 ± 2.81) mg/dl. Neonates treated by phototherapy represent N=27 (60.0%)

Table 5: Distribution of diabetic mothers according to TSB and phototherapy

Phototherapy	No.	Mean ± SD of TSB* (mg/dl)
Yes	27 (60.0%)	13.27 ± 1.70
No	18 (40.0%)	8.49 ± 1.22
Total	45 (100.0%)	11.36 ± 2.81

***** The means calculated for highest TSB readings

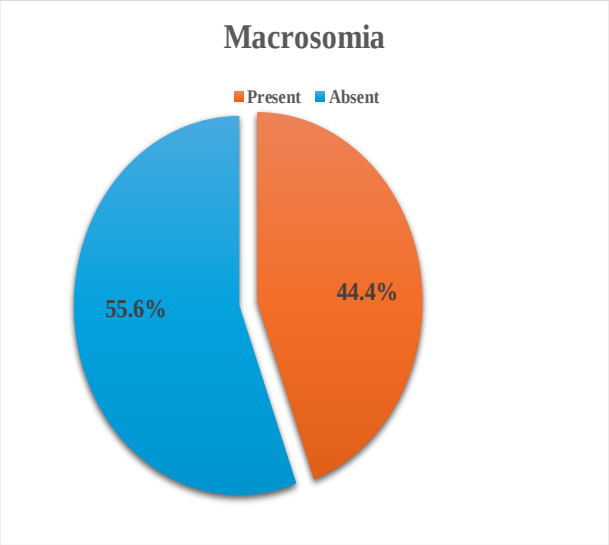

Figure 1: Distribution of neonates of diabetic mothers according to macrosomia (> 4 kg) including (present and absent). Macrosomia (> 4 kg) represent N=20 (44.4%) of neonates of diabetic mothers. (N=45)

Table 6: show distribution of neonates of diabetic mothers according to investigations including (echo study, abdominal ultrasound and brain ultrasound). Abnormal echo findings represent N=34(75.6%). Abnormal abdominal ultrasound findings represent N=9 (20.0%). Abnormal brain ultrasound represents only one patient (2.5%). In five patients neonatal brain ultrasound not done.

Table 6: Distribution of neonates of diabetic mothers according to investigations

Investigations	No.	%
Echo findings		
Abnormal	34	75.60%
Normal	11	24.40%
Total	45	100.00%
Type of abnormal Echo findings		
PDA[1]	13	38.20%
HOCM[2]	5	14.70%
PFO[3]	3	8.80%
ASD[4]	2	5.90%
ASH[5]	1	2.90%
PHT[6]	1	2.90%
MR[7]	1	2.90%
PDA/ASD	3	8.80%
PFO/ASD	1	2.90%
PFO AND VSD[8]	1	2.90%
PDA/VSD	1	2.90%
PDA/PFO/LVH[9]	1	2.90%
ASD/VSD/PDA	1	2.90%
Total	34	100
Abdominal US		
Abnormal	9	20.00%
Normal	36	80.00%
Total	45	100.00%
Type of abnormal abdominal US		
Hydronephrosis	7	77.80%
Splitting of PCS[10]	1	11.10%
Reflux Nephropathy	1	11.10%
Total	9	100.00%
RDS		
Present	23 (51.1)	9 (20.0)
Absent	22 (48.9)	36 (80.0)
Total	45 (100.0)	45 (100.0)
Brain US		
Abnormal	1	2.50%
Normal	39	97.50%
Total	40	100.00%

1. PDA: Patent ductus arteriosus, 2. HOCM: Hypertrophic obstructive cardiomyopathy, 3. Patent foramen ovale, 4. ASD: Atrial septal defect, 5. ASH: Atrial septal hypertrophy, 6. PHT: Pulmonary hypertension, 7. MR: Mitral regurgitation, 8. VSD: Ventricular septal defect, 9. LVH: Left ventricular hypertrophy, 10, PCS: Pelvicalyceal system

Cord Blood C-Peptide and Neonatal Complications

C-peptide levels were significantly higher in neonates with macrosomia (3.88 ± 1.11 nmol/L, $p < 0.001$), hypoglycemia (3.51 ± 1.17 nmol/L, $p < 0.001$), and RDS (3.37 ± 1.22 nmol/L, $p = 0.005$) (Table 7). No significant differences were noted with hypocalcemia or polycythemia.

Table 7: Mean cord blood C-peptide levels by neonatal complications (N=45)

Neonatal complications		No.	Cord blood C-peptide level (nmol/l) Mean ± SD	P-value
Macrosomia (>4kg)	Present	20	3.88 ± 1.11	<0.001*
	Absent	25	2.33 ± 0.30	
Hypoglycemia at 1st hr	Present	26	3.51 ± 1.17	<0.001*
(RBS ≤ 40 mg/dl)	Absent	19	2.35 ± 0.39	
Hypocalcemia	Present	27	3 ± 1.22	0.904
(Serum Ca <8.5mg/dl)	Absent	18	3.04 ± 0.88	
Polycythemia	Present	24	3.23 ± 1.27	0.151
(PCV ≥ 65 %)	Absent	21	2.78 ± 0.80	
Echo study	Abnormal	34	3.14 ± 1.16	0.215
	normal	11	2.66 ± 0.75	
Signs of respiratory distress (RR > 60/minute)	Present	26	3.37 ± 1.22	0.005*
	Absent	19	2.54 ± 0.65	

*P value ≤ 0.05 was significant

ROC curve analysis (figure 2) showed that C-peptide ≥2.55 nmol/L predicted hypoglycemia with 80.8% sensitivity, 68.4% specificity, and overall accuracy 75.6% ($p < 0.001$) (Table 8).

Table 8: The sensitivity, specificity and overall accuracy of Cord blood C-peptide level (nmol/l) among neonates of diabetic mothers to predict hypoglycemia at 1st hr (N=45)

Study variable	Cutoff value	Sensitivity	Specificity	Overall accuracy	P-value
Cord blood C-peptide level (nmol/l)	≥ 2.55	80.8%	68.40%	75.60%	<0.001*

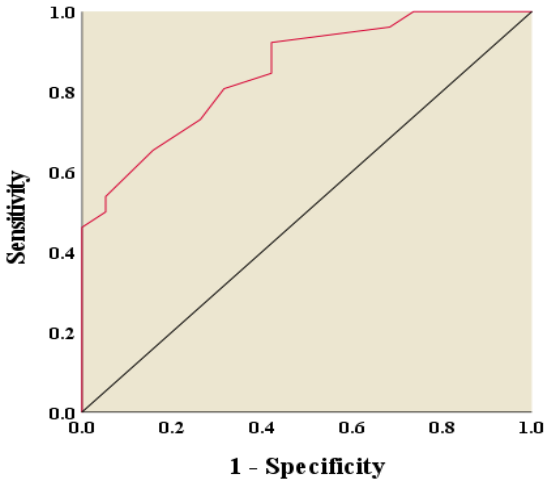

Figure 2: ROC curve for sensitivity and specificity of Cord blood C-peptide level (nmol/l) among neonates of diabetic mothers to predict hypoglycemia at birth (N=45)

For RDS, C-peptide ≥2.55 nmol/L had 73.9% sensitivity, 54.5% specificity, and 64.4% accuracy ($p = 0.009$) (Table 9).

Table 9: Sensitivity, specificity and overall accuracy of Cord blood C-peptide level (nmol/l) among neonates of diabetic mothers to predict RDS.

Study Variable	Cutoff value	Sensitivity	Specificity	Overall accuracy	P-value
Cord blood C-peptide level (nmol/l)	≥ 2.55	73.9%	54.5%	64.4%	0.009*

*P value ≤ 0.05 was significant

Table 10 shows non-significant model to predicted need for phototherapy with ($p = 0.113$).

Table 10: Sensitivity, specificity and overall accuracy of Cord blood C-peptide level (nmol/l) among neonates of diabetic mothers to predict need for phototherapy

Study Variable	Cutoff value	Sensitivity	Specificity	Overall accuracy	P-value
Cord blood C-peptide level (nmol/l)	≥ 2.55	66.7%	50%	60%	0.113*

*P value ≤ 0.05 was significant

A cutoff of ≥2.75 nmol/L predicted macrosomia with 100% sensitivity, 65.8% specificity (p = 0.004) (Table 11).

Table 11: Sensitivity, specificity and overall accuracy of Cord blood C-peptide level (nmol/l) among neonates of diabetic mothers to predict macrosomia

Study variable	Cutoff value	Sensitivity	Specificity	Overall Accuracy	P-value
Cord blood C-peptide level (nmol/l)	≥ 2.75	100%	65.8%	71.1%	0.004*

*P value ≤ 0.05 was significant

Discussion

Diabetes mellitus is the most common medical complication during pregnancy and remains a major determinant of neonatal morbidity, with outcomes strongly influenced by the duration, severity, and quality of glycemic control during pregnancy [13]. This study highlights the relationship between common neonatal complications in infants of diabetic mothers (IDMs) and umbilical cord blood C-peptide levels as a marker of fetal hyperinsulinemia. Gestational diabetes mellitus constituted a substantial proportion of cases in this study, with maternal age comparable to previously reported regional studies [14,15]. Macrosomia was a frequent finding among IDMs and was significantly associated with elevated cord blood C-peptide levels, in agreement with multiple earlier studies [16,17]. This supports the established association between intrauterine hyperinsulinemia and excessive fetal growth and fat deposition [18]. Neonatal hypoglycemia was one of the most common complications and showed a strong and statistically significant association with higher cord blood C-peptide levels, consistent with previous reports of Roodpeyma S. *et al* and Liu Y. *et al* [19, 20]. This finding reflects persistent fetal hyper-insulinemia and suggests suboptimal glycemic control, particularly during late pregnancy. Polycythemia was commonly observed but did not show a statistically significant association with cord blood C-peptide levels, a finding comparable to some previous studies [16, 21]. This suggests that factors such as chronic intrauterine hypoxia, timing of cord clamping and milking of the cord may play a more prominent role than fetal insulin levels alone. Hyperbilirubinemia and the need for photo-therapy were more frequent among IDMs and demonstrated a positive correlation with cord blood C-peptide levels, although statistical significance was limited. These findings are consistent with earlier studies and may be related to increased red cell mass and delayed feeding in this population [16, 22]. Hypocalcemia was a common but transient biochemical abnormality and was not significantly associated with cord blood C-peptide levels. This complication is likely related to maternal calcium metabolism and temporary neonatal parathyroid dysfunction rather than fetal hyperinsulinemia [23]. Respira-tory distress occurred frequently and was significantly associated with elevated cord blood C-peptide levels, supporting previous evidence that fetal hyperinsulinemia delays surfactant synthesis and lung maturation [24, 25]. The high incidence of congenital heart disease among

IDMs, particularly patent ductus arteriosus, may further contribute to respiratory compromise. Overall, the findings reinforce the clinical value of umbilical cord C-peptide as an early indicator of fetal hyperinsulinemia and its association with several important neonatal complications in infants of diabetic mothers.

Conclusion

Elevated umbilical cord C-peptide levels were significantly associated with macrosomia, hypoglycemia, hyperbilirubinemia, and respiratory distress in infants of diabetic mothers. Cord blood C-peptide may serve as an early predictor of neonatal complications and help identify infants requiring closer monitoring.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this manuscript.

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