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Role of Umbilical Cord C- Peptide Level in Early Detection of Hypoglycemia in Infant of Diabetic Mother

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ABSTRACT

Background: Until date, diabetes during pregnancy has been linked to an increased risk of maternal, fetal, and neonatal morbidity and mortality. Infants of diabetic mothers (IDM) frequently have difficulties related to fetal hyperglycemia and hyperinsulinemia caused by maternal hyperglycemia. Because insulin breakdown is accelerated in the presence of mild hemolysis, cord serum C-peptide levels are utilized as an indicator of fetal beta-cell function rather than insulin levels. **Objective:** To study the relationship between umbilical cord C-peptide and risk of hypoglycemia in infants of diabetic mothers.

Patients and Methods: This Cross-sectional study was conducted on 50 infants of diabetic mothers. Infants who developed hypoglycemia in first 24-hour age were considered as cases and infants who did not develop hypoglycemia during the first 24 hours were considered as controls in Neonatal Unit of Benha university hospitals in cooperation with the Department of Obstetrics and Gynecology, during the period from January 2022 to July 2022. **Result**: The infants were divided into two groups: Hypoglycemia group (Cases group): included 31 infants of diabetic mothers who developed hypoglycemia in first 24-hour age. normoglycemic group (Control group): included 19 infants who did not develop hypoglycemia during the first 24 hours.

Conclusion: In this study, we discovered a substantial rise in UC C-peptide levels in hypoglycemic babies as compared to the control group, indicating that C-peptide might be utilized as an early predictor of hypoglycemia in IDMs.

Keywords: Infant of diabetic mother, Hypoglycemia, Umbilical cord C peptide.

INTRODUCTION

Diabetes during pregnancy has previously been linked to an increased risk of maternal, fetal, and neonatal morbidity and mortality [(1)]. Infants of diabetic mothers (IDM) frequently have difficulties related to fetal hyperglycemia and hyperinsulinemia caused by maternal hyperglycemia [(2)].

Maternal hyperglycemia during the first trimester might result in spontaneous miscarriages or significant birth abnormalities such as truncus arteriosus or aortic coarctation. Maternal hyperglycemia can produce fetal hyperglycemia and hyperinsulinemia in the second and third trimesters, resulting in post-natal neonatal hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia, septal cardiac hypertrophy, delayed lung maturation, and macrosomia. As a result, hyperinsulinemia is a key factor in the development of numerous problems in IDM [(3)].

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Human C-peptide is a 31 amino acid chain that is released in an equimolar ratio with insulin by pancreatic beta cells. Because insulin breakdown is accelerated in the presence of mild hemolysis, cord serum C-peptide levels are utilized as an indicator of fetal beta-cell function rather than insulin levels. The purpose of this study was to investigate the link between umbilical cord C-peptide and the risk of hypoglycemia in diabetes mothers' newborns [(4-8)].

Therefore, this research aimed to study the relationship between umbilical cord C-peptide and risk of hypoglycemia in infants of diabetic mothers.

PATIENTS AND METHODS

This Cross-sectional study was conducted on 50 infants of diabetic mothers who developed hypoglycemia in first 24-hour age were considered as cases and infants who did not develop hypoglycemia during the first 24 hours whether admitted or not were considered as controls in Neonatal Unit of Benha university hospitals in cooperation with the Department of Obstetrics and Gynecology, during the period from January 2022 to July 2022.

Inclusion criteria:

- Infants of diabetic mothers.
- Both sexes were included.
- Full term and preterm.

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Exclusion criteria:

- Perinatal asphyxia.
- Severe birth defects or congenital anomalies.
- Babies need inotropes.

All studied cases were subjected to the following:

A. Full history taking and clinical examination stressing on:

1. Maternal history:

- Maternal age, gestational age, maternal weight).
- Type and duration of DM (diabetes mellitus and control).
- Mode of delivery (vaginal or cesarean section).
- Maternal diseases such as pre-eclampsia, premature rupture of membranes (PROM), mode of delivery.
- Maternal drugs for the control of DM.
- Presence of meconium in the amniotic fluid.

2. Neonatal data:

- Gender.
- Neonatal birth weight.
- Apgar score at 1 min and at 5 min.
- Causes of admission to NICU.
- Family history of diabetes mellitus.
- Birth injuries, and detailed systemic examination were recorded.
- Observation for any hypoglycemia manifestations as (irritability, jitteriness, and convulsions).

Furthermore, blood glucose (BG) measurements were performed at birth, after 30 min, and after 1, 3, 6, 12, 18, and 24 h; follow-up BG evaluations were performed until BG was normalized. Blood glucose value of < 2.6 mmol/l was considered as neonatal hypoglycemia.

B. Investigations:

- Complete blood count at day of admission.
- capillary Blood glucose(Method of assay or instrument used) at birth ,30min ,1, 3 ,6, 12, 18 and 24 hours of life.
- Umbilical cord c peptide immediately after delivery.

Approximately 3 mL of UC blood were drawn immediately after delivery from all infants who met the inclusion criteria. The blood was chilled to 4 °C, centrifuged as soon as possible, and stored at - 84 °C. UC serum C-peptide was measured using a third-generation enzyme linked immunosorbent assay (ELISA) (Modular Analytics E170, Roche Diagnostics, Singapore).

C. Examination:

- **General examination:**

Including: conscious level and Vital signs as pulse, blood pressure, capillary filling time, blood glucose, respiratory rate, temperature and head to foot examination.

- **Local systematic examination:**
  - **Cardiovascular System**: For detection of any abnormal heart sounds or murmurs.
  - **Respiratory System**: For detection of any abnormal breath sound, adventitious sounds and respiratory distress.
  - **Gastrointestinal Tract (GIT) and Abdomen**: Presence of organomegaly
  - **Central Nervous System** (CNS) and Musculoskeletal System Assessment of Glasgow coma score, pupillary reaction, examination of motor system including power, tone and reflexes.

Ethical Consideration:

Ethical permission for the study was obtained from the parents, who were fully informed about all study protocols and gave their agreement prior to enrolling their children in the study. The ethical committee of Benha University's college of medicine approved this study. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical analysis

SPSS v26 was used to conduct the statistical analysis (IBM Inc., Armonk, NY, USA). The Shapiro-Wilks test and histograms were employed to assess the normality of the data distribution. The unpaired student t-test was used to assess quantitative parametric data, which were provided as mean and standard deviation (SD). The Mann Whitney-test was used to assess quantitative non-parametric data, which were provided as the median and interquartile range (IQR). When appropriate, qualitative data were provided as frequency and percentage (%) and evaluated using the Chi-square test or Fisher's exact test. Statistical significance was defined as a two-tailed P value of 0.05.

RESULTS

Maternal age, weight, gestational age, mode of delivery, type and control of DM were insignificantly different between the studied groups. **[Table1].**

Table (1): Maternal demographic data of the studied groups

		Hypoglycemia group (n=31)	Normoglycemia group (n=19)	P value
Maternal age (years)	**Mean ± SD**	32.4 ± 6.15	34.1 ± 6.18	0.349
	Range	20 - 45	22 - 41	
Maternal weight (Kg)	**Mean ± SD**	84.7 ± 10.34	81.2 ± 11.31	0.268
	Range	68 - 102	65 - 100	
Gestational age (Months)	**Mean ± SD**	36.5 ± 1.69	35.4 ± 2.61	0.078
	Range	32 - 39	30 - 39	
Mode of delivery	**CS**	24 (77.42%)	12 (63.16%)	0.276
	NVD	7 (22.58%)	7 (36.84%)	
Type of DM	**Type 1**	2 (6.45%)	0 (0%)	0.427
	Type 2	18 (58.06%)	10 (52.63%)	
	Gestational DM	11 (35.48%)	9 (47.37%)	
Control of DM	**Insulin**	29 (93.55%)	19 (100%)	0.519
	Diet	2 (6.45%)	0 (0%)	

Birth weight was significantly higher in hypoglycemia group than normoglycemia group (P value <0.001). Sex was insignificantly different between the studied groups. **[Table 2]**

Table (2): Neonates demographic data of the studied groups

		Hypoglycemia group (n=31)	Normoglycemia group (n=19)	P value
Sex	**Male**	20 (64.52%)	11 (57.89%)	0.640
	Female	11 (35.48%)	8 (42.11%)	
Birth weight (kg)	**Mean ± SD**	3.4 ± 0.56	2.6 ± 0.74	**<0.001***
	Range	1.9 - 4.37	1.54 - 4.34	

Apgar score at 1 and 5 min was insignificantly different between the studied groups. **[Table 3]**

Table (3): Apgar score of the studied groups

		Hypoglycemia group (n=31)	Normoglycemia group (n=19)	P value
Apgar score at 1 min	**Mean ± SD**	6.6 ± 1.2	6.4 ± 1.57	0.593
	Range	4 - 9	4 - 9	
Apgar score at 5 min	**Mean ± SD**	9.2 ± 0.7	8.9 ± 1.08	0.333
	Range	8 - 10	7 - 10	

TLC and platelets were insignificantly different between the studied groups. HCT was significantly higher in hypoglycemia group than normoglycemia group (P value <0.001). **[Table 4]**

Table (4): Laboratory investigation at day of admission of the studied groups

		Hypoglycemia group (n=31)	Normoglycemia group (n=19)	P value
TLC ($x10^3$/µl)	**Mean ± SD**	12.3 ± 3.01	14.8 ± 3.51	0.132
Platelets (cells/µl)	**Mean ± SD**	240.3 ± 58.41	246.7 ± 61.33	0.796
HCT (%)	**Mean ± SD**	59.1 ± 4.78	53.7 ± 4.35	**<0.001***

Umbilical cord c-peptide was significantly higher in hypoglycemia group than normoglycemia group (P value <0.00). **[Table 5, Figure 5]**.

Table (5): The relationship between umbilical cord C-peptide and risk of hypoglycemia of the studied groups

		Hypoglycemia group (n=31)	Normoglycemia group (n=19)	P value
Umbilical cord c-peptide (ng/ml)	**Mean ± SD**	5.2 ± 0.54	1.8 ± 0.44	**<0.001***
	Range	3.9 - 5.9	1 - 3.2	

DISCUSSION

In the current study, maternal age, weight, gestational age, mode of delivery, type and control of DM were insignificantly different between the studied groups. Maternal risk factors (preeclampsia, anemia preeclampsia, polyhydramnios, PROM, UTI, HTN and obstructed labor) were insignificantly different between the studied groups.

In accordance with our findings, **Saber *et al.*** [2] conducted a research to assess the risk factors for hypoglycemia in diabetes mothers' babies (IDMs) and to investigate the association between umbilical cord (UC) C peptide levels and the risk of developing hypoglycemia. UC blood C-peptide levels and serial serum blood glucose levels were measured in all singleton infants delivered to diabetes moms over the research period. Mother and newborn data were gathered, including gestational age, maternal age, maternal weight, diabetes kinds and control, maternal glycated hemoglobin (HbA_{1c}), birth weight, Apgar score, and neonatal complete blood picture. According to their findings, 83 IDM satisfied the inclusion criteria and were included in this study. 54 (65.06%) had hypoglycemia, whereas 29 (34.94%) stayed normal. There were no significant variations in maternal or newborn differences between hypoglycemia and normoglycemic IDMs, regardless for kinds of maternal diabetics (P value = 0.41), length of diabetes (P value = 0.43), or diabetes management parameters (P value = 0.62) [2].

Also, the demographic characteristics of the mothers were similar in hypoglycemic and normoglycemic groups, such as maternal age, maternal weight, and type and duration of diabetes, **Begum *et al.*** [9] found similar results when they investigated the association between umbilical cord C-peptide and the risk of hypoglycemia in diabetes mothers' newborns. The study included 60 neonates born to diabetes moms. Cases were 30 newborns that suffered hypoglycemia at any point within their first 24 hours of life. Another 30 newborns were included as controls since they did not develop hypoglycemia within the first 24 hours. C-peptide levels in the umbilical cord were measured in both groups. At 4, 6, 8, 12, 18, and 24 hours of life, all newborns were tested for hypoglycemia. Hypoglycemia was defined as a blood glucose level of less than 2.6 mmol/l.

In contrast, **Agrawal *et al.*** [11] investigated whether umbilical cord blood glucose corresponds with future hypoglycemia after birth in babies of diabetes women who are well-controlled. Thirty-eight term babies born to diabetes moms who were well-controlled were included in the study. Diabetes was already present in five of the moms. 16 of the 33 gestational diabetes moms were handled with insulin, whereas 17 were controlled with diet. During labour and delivery, maternal blood glucose levels were kept between 4 and 8 mmol/L. The glucose hexokinase technique was used to assess infants' plasma glucose levels from venous cord blood at less than 30 minutes, 1 hour, and 2 hours of life. They discovered that IDMs with hypoglycemia had considerably longer periods of maternal diabetes [11].

The birth weight was substantially greater in the hypoglycemia group than in the normoglycemia group in the current study (P value 0.001). The gender differences between the groups tested were minor. **Saber *et al.*** [2] showed that IDM with hypoglycemia had greater birth weights (3.90±0.81) kg than IDM with normoglycemia (3.78±0.49) kg, which is consistent with our findings.

Furthermore, **Agrawal *et al.*** [11] discovered that hypoglycemic newborns were considerably heavier at birth than non-hyperglycemic neonates (P value 0.05). **Metzger *et al.*** [12] also discovered that children with a greater birth weight were more likely to suffer hypoglycemia and hyperinsulinemia than the control group with a normal birth weight, implying physiologic links between maternal hyperglycemia and fetal insulin production.

Furthermore, **Dawid *et al.*** [13] investigated if there is a link between maternal glycated haemoglobin, cord blood insulin level, and overall condition in diabetes mothers' newborns. In their study, 158 diabetes mothers' neonates (86 G1, 56 G2, 16 P) and 171 healthy mothers' newborns were assessed. They found that the diabetes group had a greater mean birth weight (3199 +/- 617 g) than the control group (2885 +/- 905 g).

Begum *et al.* [9], on the other hand, discovered that the sex of newborn children was insignificantly different between both study groups, where the birth weight was statistically significant greater in the control group than the case group. This difference may be caused by a different number of instances in both groups than the current study.

Regarding our finding, Apgar score at 1 and 5 min was insignificantly different between the studied groups.

In line with our findings, **Saber *et al.*** [2] discovered that the Apgar score at 1 and 5 minutes was not substantially different between the hypoglycemia and normoglycemia groups. Hypoglycemia was substantially greater in the hypoglycemia group than in the normoglycemia group in the current research (P value 0.001). According to **Saber *et al.*** [2], the peak of hypoglycemia in the hypoglycemic group occurred within the first 3 hours of life, with 33.11±8.84 mg/dl for the hypoglycemic group and 54.10±mg/dl for the normoglycemic group (P = 0.0001). Furthermore, the majority of the newborns (96.30%) had no

hypoglycemic manifestation, and just two patients (3.70%) experienced manifestation one, with lethargy and poor suckling [2].

Furthermore, **Begum *et al.*** [9] reported that in both groups, blood glucose level decreased rapidly after birth, then increased in both groups over the next 24 hours of postnatal period, glucose level of cases were persistently lower than that of controls with significant difference of mean blood glucose values between cases and controls at 4 hr (2.71 vs 3.38 p=0.003), 6 hr (2.71 vs 3.45 p=0.0004), and 8 hr (2.87 vs 3) [9].

HCT was considerably greater in the hypoglycemia group than in the normoglycemia group in our research (P value 0.001). In agreement with our findings, **Saber *et al.*** [2] discovered that HCT was considerably greater in the hypoglycemia group than in the normoglycemia group. According to our findings, capillary blood glucose levels were considerably lower in the hypoglycemia group than in the normoglycemia group at all time measures (P value 0.001).

Saber *et al.* [2] found that capillary blood glucose on the first day of birth was substantially lower in the hypoglycemia group than the normoglycemia group at all time measures (P-value 0.05).

Babies born to diabetes mothers are hyperinsulinemic, and neonatal hypoglycemia appears to ensue, as does a delay in rising plasma glucagon levels [7]. The C-peptide, which indicates insulin production, is directly connected to the degree of maternal diabetes and is highly correlated with newborn problems such as hypoglycemia [2].

Our results showed that the umbilical cord c-peptide was significantly higher in hypoglycemia group than normoglycemia group (P value <0.001).

In line with our findings [2], the mean (SD) of UC C-peptide in the case group was 1.73 1.07 ng/ml, ranging from 0.13 to 3.3 ng/ml, while it was 1.08 0.81 ng/ml, ranging from 0.25 to 3.9 ng/ml in the control group; there was a statistically significant difference between the two studied groups (P value = 0.005) [2].

Begum *et al.* [9] found that the majority of newborns in cases (66.7%) and 40% of controls had cord C-peptide levels higher than the typical reference range of 0.8 to 3ng/ml. However, the mean umbilical cord serum C-peptide level in IDMs (4.57) was considerably greater (P value 0.005) than in control newborns (2.81).

This conclusion is also consistent with earlier research that found cord C-peptide levels to be negatively associated to blood glucose levels in the early postnatal period [12]. Additionally, elevated UC C-peptide levels have been linked to newborn macrosomia [12], and neonatal septal hypertrophic cardiomyopathy. As a result, hyperinsulinemia is a key factor in the development of numerous problems in IDM [3].

Abdelgadir *et al.* [15] observed a similar finding [15]. This statistically significant difference in mean C-peptide value suggests that there may be a link between high C-peptide and the risk of hypoglycemia in IDMs.

C-peptide concentration has the potential to be used as a marker to predict pediatric metabolic outcomes. Furthermore, measuring C-peptide concentrations may enhance risk classification in neonates delivered to obese or diabetic moms, allowing for more targeted resource allocation to those who are most vulnerable. Prior study has attempted to shed light on this issue by investigating the relationship between C-peptide concentration and maternal BMI, diabetes [4], gestational weight gain [17], and fetal overgrowth [12]. However, therapeutic relevance of these relationships is still a long way off. Furthermore, a few population-based studies were done to examine the feasibility of measuring C-peptide concentrations in pregnant women [18].

CONCLUSIONS

In this study, we discovered a statistically significant increase in UC C-peptide levels in infants who developed hypoglycemia when compared to the control group in this study, implying that C-peptide can be used as an early predictor of hypoglycemia in IDMs and as a predictor of babies who require neonatal admission.

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