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Comparative Analysis of Carnitine Levels in Pregnant Women With and Without Gestational Diabetes

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ABSTRACT

Background:

The global prevalence of gestational diabetes ranges from 1% to 20% and is rising, reaching 8.9%–53.4% due to updated screening and diagnostic criteria. Carnitine plays a key role in energy metabolism by transporting long-chain fatty acids into mitochondria. Its deficiency may impair lipid metabolism and contribute to the development of gestational diabetes.

Aims of study:

To determine the relationship between carnitine and gestational diabetes versus normal pregnancy.

Materials & Methods:

A one-year case-control study was conducted at Salahaddin General Hospital, involving 87 pregnant women (≥28 weeks, singleton viable pregnancies). The participants were divided into two groups: 32 women with gestational diabetes (case group) and 55 healthy controls matched by age and gestational age. Blood samples (4 ml) were collected from all participants to measure carnitine levels.

Results:

In this study, carnitine level was significantly decreased in patients with gestational diabetes when compared with controls. Carnitine level < 23.56 µmol/L is a predictor for gestational diabetes.

Conclusions:

Use of carnitine level as a screening tool helps predict the susceptibility of high risk pregnant women for development of gestational diabetes, which affects the development of pregnancy and the growth of the fetus and can be relied upon to reduce future complications of diabetes.

INTRODUCTION:

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both (1). It includes Type 1 DM (T1DM), which results from autoimmune destruction of pancreatic β-cells; Type 2 DM (T2DM), characterized by insulin resistance with progressive β-cell dysfunction; Gestational Diabetes Mellitus (GDM), defined as glucose intolerance first recognized during pregnancy; and other forms such as monogenic diabetes, diabetes due to pancreatic diseases, and drug-induced diabetes. The global prevalence of diabetes is expected to reach 642 million by 2040 (1).

Gestational Diabetes Mellitus is the most common cause of hyperglycemia in pregnancy, accounting for approximately 84% of cases. Major risk factors include obesity, advanced maternal age, a family history of diabetes, dyslipidemia, vitamin D and C deficiency, and poor dietary habits. Diagnosis is typically established using the Oral Glucose Tolerance Test (OGTT) between 24 and 28 weeks of gestation (2).

The pathophysiology of GDM is primarily driven by insulin resistance caused by placental hormones such as human placental lactogen, progesterone, and cortisol. These hormones antagonize insulin action, leading to maternal hyperglycemia. As a consequence, excess glucose crosses the placenta, resulting in fetal hyperinsulinemia, which contributes to macrosomia and other pregnancy-related complications (3).

The global prevalence of GDM ranges from 1% to 20%, with the highest prevalence reported in Southeast Asia (24.2%) and the lowest in Africa (10.5%). In Iraq, the prevalence of GDM has been reported to reach 13.3%, reflecting regional variations in risk factors and screening practices (4).

Diagnosis of GDM is based on WHO and FIGO criteria using a 75-g OGTT. In addition to glucose testing, biomarkers such as HbA1c, placental protein 13 (PP13), and pentraxin-3 (PTX3) have been suggested as potential predictors for the early detection and risk assessment of GDM (5).

Preconception glycemic control is associated with a reduced risk of miscarriage and congenital malformations (6). Lifestyle modification remains the cornerstone of GDM prevention and management, including adherence to a healthy diet and engaging in at least 30 minutes of daily physical activity (7). When lifestyle measures are insufficient, insulin is the first-line pharmacological treatment, while metformin and glyburide may be considered as alternative therapies in selected cases (8). Postpartum follow-up is essential, as most women return to normoglycemia after delivery; however, an OGTT is recommended at 4–12 weeks postpartum and subsequently every 1–3 years due to the increased risk of future diabetes (9).

GDM is associated with several maternal complications, including preeclampsia, increased rates of cesarean delivery, higher cardiovascular risk, postpartum depression, and an elevated likelihood of developing Type 2 DM later in life (10). Fetal and neonatal complications include macrosomia, neonatal hypoglycemia, jaundice, hypocalcemia, respiratory

distress syndrome, and long-term risks such as obesity and Type 2 DM (11).

Carnitine plays a vital role in the transport of long-chain fatty acids into mitochondria for β-oxidation. During pregnancy, carnitine levels decrease, which may exacerbate insulin resistance. Elevated acyl-carnitine levels have been associated with β-cell dysfunction and the pathogenesis of GDM (12). Carnitine supplementation has been suggested to improve lipid metabolism and may reduce the risk of fetal macrosomia, although further studies are required to confirm its clinical benefits (13).

MATERIALS AND METHODS

Study design, setting, and data collection period:

This case–control study was conducted in the Department of Obstetrics and Gynecology at Salahaddin General Hospital, Salahaddin Governorate, over a period of one year.

Study participants and sample size:

Initially, the study included 96 pregnant women with singleton pregnancies, a viable fetus, and a gestational age of ≥ 28 weeks. All participants were informed about the nature of the study, and verbal consent was obtained. Nine participants had invalid or missing carnitine results and were excluded; therefore, data from 87 pregnant women were included in the final analysis. The participants were divided into two groups: a case group consisting of 32 pregnant women diagnosed with gestational diabetes mellitus (GDM) and a control group consisting of 55 healthy pregnant women without complaints, matched with the case group for age and gestational age. The diagnosis of GDM had been confirmed during antenatal care visits earlier in pregnancy. Gestational age was calculated based on the first day of the last menstrual period and confirmed by early abdominal ultrasound examination.

Inclusion and exclusion criteria:

The case group included women with singleton pregnancies, viable fetuses, gestational age ≥ 28 weeks, and a diagnosis of gestational diabetes mellitus. The control group included women with single, uncomplicated pregnancies at ≥ 28 weeks of gestation. Exclusion criteria for both groups included multiple pregnancies, overt diabetes mellitus, and the presence of gestational hypertension or pre-eclampsia.

Data collection tools and clinical assessment:

Data were collected using a structured questionnaire administered to all enrolled pregnant women. The questionnaire included information on age, socioeconomic status, and educational level, as well as obstetric history (parity, last menstrual period, and gestational age) and past medical history. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²) (14). Weight and height were measured using the same scale for all participants. Based on BMI, participants were classified as normal (≤ 24.99 kg/m²), overweight (25–29.99 kg/m²), or obese (≥ 30 kg/m²). A general physical examination was performed for all participants, including measurement of vital signs and specific obstetric assessments such as symphysis–fundal height to detect polyhydramnios and large-for-gestational-age (macrosomic) fetuses. Laboratory investigations included fasting blood sugar (FBS), random blood sugar (RBS), oral glucose tolerance test (OGTT), and

measurement of maternal serum carnitine levels.

Sample collection and carnitine assay:

A total of 4 mL of venous blood was drawn from the volar surface of the forearm of each participant at presentation for the assessment of carnitine levels. The assay is based on the transfer of an acetyl group from coenzyme A (CoA) to carnitine, producing free CoA, which is subsequently processed with oxidation of the Oxi-Red probe, resulting in measurable fluorescence (excitation/emission at 535/587 nm) and absorbance at 570 nm. The assay range for serum carnitine was 20–100 µmol/L.

Ethical considerations and official approvals:

Verbal consent was obtained from all participants prior to data collection. Participant anonymity was maintained by removing names and assigning identification codes. All collected data were kept confidential, stored on a password-protected laptop, and used exclusively for research purposes. Administrative and ethical approvals were obtained from the Council of the Iraqi Board of Medical Specialization and from the Department of Obstetrics and Gynecology at Salahaddin General Hospital.

Statistical analysis:

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26. Continuous variables were presented as means, standard deviations, and ranges, while categorical variables were presented as frequencies and percentages. An independent two-tailed t-test was used to compare continuous variables between groups. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of maternal carnitine levels as a diagnostic marker for GDM. A p-value of less than 0.05 was considered statistically significant.

RESULTS:

GDM is associated with profound changes in metabolism. Free carnitine (C0) has a critical role in energy metabolism of transporting long-chain fatty acid from the cytosol into the mitochondria, which results in C0 transforming into acyl carnitine (AC) [15].

The result In Table 2 showed the current results showed a significant difference in the means of FBS and RBS between case and control groups (P= 0.001 and 0.001, respectively).

The result In Table 3 revealed that Carnitine level was significantly decreased in patients with GDM when compared with controls (P= 0.013). Moreover, carnitine level < 23.56 µmol/L is a predictor for GDM.

DISCUSSION

Carnitine deficiency is a serum C0 level < 20 µmol/L. C0 deficiency might impair lipid metabolism resulting in GDM. Evaluated circulating AC (such as C3 and C5) is associated with GDM and induces pancreatic β-cell dysfunction. A previous study proposed that C0 and AC decreased in pregnancy in the first trimester compared with non-pregnancy [16]. In the current study, 87 pregnant women with singleton pregnancy were recruited, 32 of them had confirmed GDM (Case group or GDM group, 36.8%) and the other 55 (63.2%) did not (Control group).

By comparison to other studies, a close findings observed in Herrera Martinez et al study in 2018, as reported that mean and SD of the age was 33.08 ± 4,78 years, in which those aged more than 35 years represented the highest proportion (38%). Moreover, history of T2DM found in majority of patients (76.1%), previous GDM found in 24.2% of them [17].

Another close results observed in Smith et al study in 2018, in which the mean and SD of age of pregnant women was 32.4 ± 5.97 years, a lower percentage of overweighed pregnant women were participated (27.1%) and hypertension existed in 26.7% of the participants [18].

Also, a close finding observed in Farias et al study in 2017, when reported that women had a mean age of 26.8 (SD: 5.5) years and an early pregnancy BMI of 25.4 (SD: 4.6) kg/m² at the study baseline.

About 40.4% were classified as overweight or obese, 6.0% smoked during the 1st trimester, and 56.3% reported >8 years [19].

The present work revealed a non-significant difference between the study groups by age (P= 0.524), BMI (P= 0.282), GA (P= 0.973), and parity (P= 0.703).

By comparison to Dong et al study in 2020, an agreement reported, as found that there were no significant differences in maternal age, gestational age at diagnosis of GDM, BMI and parity between those with GDM and control group (P>0.05) [20].

In the same manner, Ali M et al study in 2013, shows no significant difference in the mean maternal age, parity & BMI between the study groups, P = 0.065, 0.486, 0.97 respectively [21]. Differently, Dudzik et al study in 2018, the results obtained revealed a non-significant difference in age, parity or blood pressure between the women in participated in the study, BMI before gestation was similar in control and GDM women, despite a significantly higher BMI in 2nd trimester (P<0.05) [22].

The difference reported above related to different sample size and different study design. Additionally, educational level, ethnic and socioeconomic factors were among the factors determine the difference reported above.

By comparison to Dudzik et al study in 2018, the results obtained agreed to the current one in that women who were classified as GDM according to WHO-criteria, had significantly higher fasting glucose, and HbA1c than controls (P<0.05) [22].

While Dong and colleagues in a study conducted in 2020, contradict the current finding in that of oral glucose tolerance test, FBS and HbA1c was not significantly different between study groups (P>0.05) [76], which agreed to the study done by Ali M et al study in 2013, in which no significant difference in the mean level of FBG, RBG and the HbA1c between the study groups (P = 0.6, 0.403, 0.420. respectively) [21].

Differences observed above related to the different sample size and to educational level of the participants, it had been reported that pregnant women with a high education level and persistent work during pregnancy have better self-discipline and compliance. These women will consider less consumption factors and are willing to purchase a blood glucose meter, and record dietary diaries to

complete self- glucose monitoring and dietary control.

The GDM can cause short-term and long-term adverse effects in pregnant women, as an increased risk of macrosomia, preterm delivery, preeclampsia, cesarean section, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, metabolic disorders, and even cardiovascular disease [20].

Moreover, it also has a far-reaching effect on the health of offspring. Frequent data have shown that maternal hyperglycemia is positively correlated to health problems in offspring, as an elevated incidence of obesity, T2DM, metabolic syndrome (a cluster of conditions that occur together, increasing risk of heart disease, stroke, type2 DM), hypertension, dyslipidemia, insulin resistance (IR), cardiovascular disease or autism [23].

Sun and colleagues in their study in 2020 agreed to the current results, as they reported that Carnitine deficiency was significantly reported in pregnant women with GDM, and abnormal metabolism of blood glucose and lipid was accompanied by GDM ($P < 0.05$) [24].

In the same accordance, Agakidou et al study, in which 54 pairs of mothers (27 with GDM and 27 with normal pregnancies) and 26 non-pregnant controls.Their results revealed in comparison to the controls, both maternal groups had significantly lower free carnitine, whereas the non-GDM but not the GDM mother had significantly lower acylcarnitine ($P < 0.05$), concluded that Well controlled GDM does not exacerbate changes in free carnitine, acyl-carnitine, and fatty acid levels in pregnant women [25].

Differently, Pappa and other co-authors reported a different result, they found that both groups of uncomplicated pregnancy and those with GDM groups had low levels of total carnitine compared to control group (non-pregnant), but surprisingly, the GDM group did not exhibit any further decrease of carnitine levels, as would have been expected by the combination of pregnancy and diabetes [26].

The plausible explanation for the difference reported above is either statistical in form of different sample size or status of the pregnancy, presence of pre-pregnancy diabetes, history of previous GDM, the severity of GDM, type of management used, since the good glycemic control of maternal diabetes, which provided a metabolic balance similar to that of normal pregnancy and method used to assess level of carnitine, as different assay (radioisotopic) used by other studies include measurements in plasma instead of whole blood may have contributed to the different results.

CONCLUSION

The study concluded low level of carnitine in pregnant women with gestational diabetes, so use of carnitine level as a screening tool helps predict the susceptibility of high risk pregnant women for development of gestational diabetes, which affects the development of pregnancy and the growth of the fetus and can be relied upon to reduce future complications of diabetes

RECOMMENDATION

We recommend doing carnitine test as a part of screening for pregnant women at high risk of developing gestational diabetes. Conduct more comprehensive

large studies to determine the role of carnitine in diagnosis of gestational diabetes. Also Giving L-carnitine supplements in patients at high risk of developing gestational diabetes. Lastly, Conduct more researches on the relationship of carnitine to lipid profile.

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Level (µmol/L)	GDM Mean ± SD	Control Mean ± SD	Value
	19.59 ± 7.42	27.44 ± 16.46	**0.013**

TABLES

Table 1: Distribution of the study groups by certain clinical characteristics

Demographic clinical and Characteristics	Study groups		Total (%) n= 87
	GDM (%) n= 32	Control (%) n= 55	
Age (Years)			
19 - 20	1 (3.1)	11 (20.0)	12 (13.8)
21 - 30	23 (71.9)	37 (67.3)	60 (69.0)
31 - 42	8 (25.0)	7 (12.7)	15 (17.2)
BMI Level			
Normal	3 (9.4)	10 (18.2)	13 (15.0)
Overweight	17 (53.1)	34 (61.8)	51 (58.6)
Obese	12 (37.5)	11 (20.0)	23 (26.4)
GA (Week)			
< 32	17 (53.1)	17 (30.9)	34 (39.1)
32 – 36^{+6}	11 (34.4)	16 (29.1)	27 (31.0)
≥ 37	4 (12.5)	22 (40.0)	26 (29.9)
Parity			
Nulliparous	10 (31.2)	27 (49.1)	37 (42.5)
Primiparous	9 (28.2)	9 (16.4)	18 (20.7)
Multiparous	13 (40.6)	19 (34.5)	32 (36.8)
Educational Level			
Illiterate	0 (0)	9 (16.4)	9 (10.4)
Primary School	15 (46.9)	18 (32.6)	33 (37.9)
Secondary School	4 (12.5)	14 (25.5)	18 (20.7)
Higher Education	13 (40.6)	14 (25.5)	27 (31.0)
Family History			
Positive	19 (59.4)	16 (29.1)	35 (40.2)
Negative	13 (40.6)	39 (70.9)	52 (59.8)

Table 2: Comparison between study groups by FBS and RBS levels

Parameters	Study groups		P - Value
	GDM Mean ± SD	Control Mean ± SD	
FBS (mg/dl)	97.62 ± 6.42	76.74 ± 7.99	0.001
RBS (mg/dl)	130.93 ± 21.55	96.58 ± 8.82	0.001

Table 3: Comparison between study groups by carnitine level

Carnitine	Study groups	P –