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Association of Protein C and Biochemical Parameters with Miscarriage in Yemeni Gestational Diabetes Mellitus

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is a metabolic disorder associated with increased risk of maternal and fetal complications, including miscarriage. Protein C, a natural anticoagulant, has been implicated in pregnancy loss; however, its association with GDM and related metabolic abnormalities remains insufficiently investigated.

Methods: In this comparative cross-sectional study, 400 pregnant women aged 18-41 years were recruited from different hospitals and medical centers between May 2023and May 2024. The study included 200 women diagnosed with GDM and 200 normoglycemic pregnant controls. Participation was voluntary, and biochemical parameters, including protein C levels, were measured using standard laboratory methods

Results: Levels of Protein C, fasting blood sugar, random blood sugar, HbA1c, triglycerides, total cholesterol, LDL-cholesterol, BMI, TyG index, TyG-BMI index, TC/HDL-c, TC/LDL-c, creatinine, and urea were significantly higher in the GDM group compared with controls ($p < 0.001$for all), whereas HDL-cholesterol was significantly lower in the GDM group (< 0.001) .

Conclusion: The study suggests that elevated Protein C concentrations may be linked to insulin resistance in women affected by GDM, potentially contributing to an increased risk of miscarriage.

Article Info

Keywords:
Protein C, gestational diabetes, miscarriage, biochemical parameters, Yemeni women

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1. INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most frequent metabolic disorders that occur during pregnancy. It affects a substantial proportion of pregnant women worldwide, with an estimated 18.4 million cases, accounting for nearly 86.4% of all hyperglycemia cases detected during gestation [1]. GDM is defined as glucose intolerance first identified during pregnancy and may lead to short- and long-term complications for both the mother and child [2, 3]. Women with GDM are at an increased risk of developing several adverse outcomes, such as preeclampsia, preterm birth, and spontaneous miscarriage. Persistent hyperglycemia in GDM induces oxidative stress and endothelial dysfunction, disturbing the natural anticoagulant mechanisms of the body.

Physiologically, pregnancy induces a mild hypercoagulable state as a protective mechanism against hemorrhage during delivery[4]. However, in GDM, chronic hyperglycemia and oxidative stress exaggerate this response, leading to endothelial injury and an imbalance in the natural anticoagulant system[5]. Protein C, a vitamin K–dependent glycoprotein, plays a critical role in maintaining coagulation balance. Variations in Protein C levels have been observed in women with diabetes and those experiencing recurrent pregnancy loss, indicating a potential association with disturbances in placental vascular function[6]. Moreover, excessive production of reactive oxygen species (ROS) and accumulation of lipid peroxidation products have been identified in cord blood and embryonic tissues [**7-10**]. Despite this, the impact of heightened placental oxidative stress in gestational diabetes mellitus (GDM) on the redox balance of fetal en-

dothelial cells and its potential role in increasing the risk of vascular problems later in life remains insufficiently understood.[7]. In addition to changes in coagulation, GDM is marked by dyslipidemia, especially high triglyceride and LDL cholesterol levels and low HDL levels[8]. This exacerbates the vascular and placental problems. The combination of abnormal lipid metabolism, endothelial dysfunction, and hypercoagulability may increase the risk of miscarriage. Despite global evidence, there is insufficient information regarding these biochemical and coagulation changes in Yemeni women, a demographic group in which nutritional and healthcare disparities may affect pregnancy outcomes. The current study aimed to examine the association between Protein C levels and miscarriage across various trimesters in Yemeni women with gestational diabetes mellitus (GDM).

2. MATERIALS AND METHODS

2.1. DATA COLLECTION AND SUBJECTS

In the present comparative cross-sectional study, samples were collected from different hospitals and centers from 200 normal pregnant women and 200 GDM women aged18-41 years voluntary participation was managed according to the highest standards of scientific integrity. Statistical comparisons were conducted using SPSS version 22. This study starting in May 2023 until May 2024, adhering strictly to medical ethics Ethics Committee of the Faculty of Medicine and Health Sciences, Sana'a University. at the Department obstetrics' and gynecology of Al-Thawra hospital, Aljomhory hospital, Ibn Hayyan hospital, alsabin maternity and childhood

The hospitals include Matnah Bani Matar Hospital, C. Plas Hospital, Yemeni-French Hospital, Al-Mutawakel Hospital, and European Hospital, in addition to many maternity and child centers.

Participant with any chronic disease, including cardiac, liver,or renal disorders; autoimmune disease; type 1 or type 2 diabetes mellitus :or a history of miscarriage. attributed to TORCH infections were excluded from both groups

2.2. SAMPLE COLLECTION

After fasting for nine hours, 10 mL of blood was drawn from each participant to assess fasting blood sugar (FBS), HbA1C, lipid profile (total cholesterol, triglycerides, HDL, LDL), renal function (urea and creatinine), and Protein C levels using automated laboratory methods. Samples were immediately divided into three labeled Vacutainer tubes: a plain tube for biochemical assays, a trisodium citrate tube for Protein C measurement, and an EDTA tube for HbA1C analysis. An additional 2 mL of venous blood was collected for random blood glucose testing.

2.3. BIOCHEMICAL ANALYSES

Blood glucose, HbA1C, total cholesterol, triglyceride, high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), creatinine, and urea levels were measured at the National Center of Public Health Laboratories (NCPHL), Sana'a City, using -Clinical chemistry analyzer Mindray BS240.

2.4. MEASUREMENT OF PROTEIN C

Protein C levels in plasma were measured at the National Center of Public Health Laboratories (NCPHL) in Sana'a using an ELISA kit from ADA Autoimmune Diagnostic Assays (lot No: 23310) on a Mindray MR-96 A analyzer. The assay employed a sandwich ELISA format, with microplates coated with antibodies that specifically bind to human Protein C. The color change produced by the chromogen was measured at 450 nm using a spectrophotometer. Protein C concentrations in the patient samples were calculated by comparing the optical density values to a reference curve generated from the standard plasma of the kit. Normal plasma levels range from 70 to 150%.

2.5. ULTRASOUND EXAMINATION PROTOCOL

All ultrasound examinations were performed using a compatible device (e.g., a color Doppler ultrasound system). The ultrasound results were followed for 200 normal pregnant women with a normal single live fetus. In addition, 200 GDM patients showed dead fetuses.

2.6. STATISTICAL ANALYSIS

Statistical analyses were conducted using IBM SPSS Statistics software (version 27; IBM Corp., Armonk, NY, USA). Non-normally distributed continuous variables were expressed as median and interquartile range (IQR), and their differences between groups were assessed using the Mann–Whitney U test (for two independent groups) or the Kruskal–Wallis test (for more than two independent groups). The normality of the data distribution was checked before analysis. Categorical variables were summarized using frequencies and percentages. Correlations between nonparametric variables were evaluated using Spearman's rank correlation coefficients.

3. RESULTS

Table (1) shows the biochemical parameters of GDM and normal pregnancies BMI(median=27, p-value 0.001) systolic blood pressure (median=110, p-value 0.001), diastolic blood pressure(median=70, p-value 0.001) FBS (median=101 p-value = 0.001), RBS (median=173 p-value = 0.001), HbA1C (median=6.9, p-value =

Table 1. Anthropometric and Biochemical Parameters of Normoglycemic and GDM Pregnant Women

Parameters	Normal pregnant (N=200)	GDM(N = 200)	p.value
BMI	27.0 (25.3 – 28.8)	23.5(22.4 – 24.0)	0.001
Systolic blood pressure	110 (106 – 120)	106 (100 – 115)	0.001
Diastolic blood pressure	70 (70 -80)	68 (60 -75)	0.001
FBS	101 (98- 108)	70 (66 - 74)	0.001
RBS	173 (162 – 191)	115(101-125)	0.001
HbA1 C	6.9 (6.8 – 7.5)	4.6 (4.2 – 4.9)	0.001
Cholesterol	139 (125 – 150)	113 (106 -119)	0.001
Triglyceride	139 (122 – 151)	110 (102 – 116)	0.001
HDL-C	36 (32 – 39)	40 (38 – 42)	0.001
LDL-C	75 (65 – 86)	52 (48- 55)	0.001
Creatinine	0.66 (0.48 – 0.76)	0.43(0.36 – 0.53)	0.001
Urea	22.5 (15 – 33.7)	15 (12 – 20)	0.001
Protein.C	175 (166 – 184)	106 (92 -122)	0.001
TYG.index	7.1(6.3 – 7.8)	3.8 (3.5 – 4.1)	0.001
TyG.BMI.index	193 (162 – 220)	88 (79 – 96)	0.001
TC/HDL-C	3.8 (3.4 – 4.5)	2.8 (2.7 – 2.9)	0.001
TG/HDL-C	3.7 (3.2 – 4.6)	2.8 (2.6 – 2.9)	0.001

0.001), cholesterol(median=139, p-value 0.001), triglyceride (median=139, p-value = 0.001), HDL-C (median=36 p-value = 0.001), LDL-C (median=75p-value = 0.001), creatinine(median=0.66,p-value = 0.001), urea(median=22.5,p-value = 0.001, protein C (median=175 p-value = 0.001), TyG index(median=7.1 p-value = 0.001), TyG-BMI index (median=193 p-value = 0.001C/HDL-C(median=3.8 p-value = 0.001), and TG/HDL-C (median=3.7 p-value = 0.001) were found to be significantly different between the two groups. Biochemical parameters were expressed as median and interquartile range (IQR) using the Mann–Whitney U test.

Table 2 presents the Spearman correlation analysis. Protein C levels were strongly positively associated with the number of miscarriages, showing significant correlations for the first (r = 0.498, p = 0.001), second (r = 0.680, p = 0.001), and third (r = 0.481, p = 0.001) pregnancies. The correlation with a fourth miscarriage was weaker but remained significant (r = 0.126, p = 0.012). Additionally, Protein C levels were positively correlated with the number of stillbirths, with moderate correlations observed for the first (r = 0.320, p = 0.001), second (r = 0.307, p = 0.001), and third (r = 0.203, p = 0.001) events.

Fig (1) Boxplot showing the distribution of Protein C levels according to abortion status and gestational trimester. The boxes represent the interquartile range (IQR), the horizontal line inside each box indicates the median, and the whiskers show the minimum and maximum values within 1.5×IQR. Circles (°) and asterisks (*) denote outliers and extreme values, respectively.

4. DISCUSSION

Activated Protein C, produced in the liver, serves as an essential component of the body's natural anticoagulant system, helping to regulate and prevent excessive blood clot formation in vivo [9]. Protein C elevation is uncommon [10]. This condition is particularly significant during pregnancy, as the gestational period is characterized by a hypercoagulable state. Any further disruption in the balance of anticoagulant factors could intensify this tendency, potentially resulting in placental thrombosis, reduced placental perfusion, fetal demise, and recurrent pregnancy loss [11].

We compared Protein C levels in women with gestational diabetes mellitus (GDM) who experienced recurrent pregnancy loss across the first, second, and third trimesters with those of normal pregnant controls. The

Table 2. Correlation between Protein C levels and recurrent pregnancy loss

	Protein C	
N = 400	**r-Coefficient Correlation**	P .value
Miscarriage 1	0.498	0.001
Miscarriage 2	0.680	0.001
Miscarriage 3	0.481	0.001
Miscarriage 4	0.126	0.012
Stillbirth 1	0.320	0.001
Stillbirth 2	0.307	0.001
Stillbirth 3	0.203	0.001

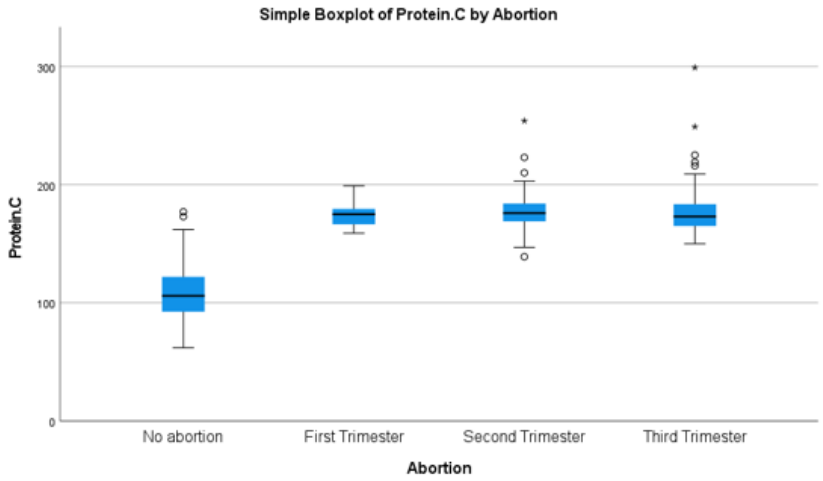

Figure 1. Boxplot showing the distribution of Protein C levels according to abortion status and gestational trimester.

results demonstrated a significant elevation in Protein C levels in women with GDM compared to those in the normal pregnant group. This is consistent with several studies, such as those in Nigeria by Obeagu et al. [10] and in Korea by Jung et al.. W I et al[12].

Insulin resistance in GDM can lead to hyperinsulinemia, endothelial dysfunction, and hypertriglyceridemia, creating a prothrombotic state[13]. Protein C levels may increase as a compensatory anticoagulant response, although this response may not fully counterbalance the increased thrombotic risk[14]. However, most studies reported that the significant reduction in Protein C levels observed in normal pregnant women was attributed to decreased activity of tissue plasminogen activator (tPA), which remained low for approximately one hour after delivery before returning to normal levels. This reduction was associated with a progressive and ultimately threefold increase in plasminogen activator inhibitor-1 (PAI-1) as well as elevated concentrations of plasminogen activator inhibitor-2 (PAI-2) O'Riordan et al and Kruithof, E. K, et al. [15, 16].

Moreover, Protein C activity increased in the first trimester compared to that in normal pregnant women, with a significant increase from the second to the third trimester. This finding is consistent with the study conducted in Korea by Jung Y. W. et al [12]. This contradicts the results reported in the Indian study by Mukhtar et al.[17]. Pathological studies have shown that during pregnancy, maternal insulin sensitivity normally decreases to provide more glucose to the fetus[18]. This resistance is driven by placental hormones such as human placental lactogen (hPL). Inflammatory and metabolic stress damage the vascular endothelium, disrupting the balance between procoagulant and anticoagulant factors. Endothelial dysfunction promotes coagulation. Insulin resistance is associated with increased prothrombotic protein production[19]. As Protein C is part of the anticoagulant defense system, its downregulation or functional inhibition could favor a hypercoagulable state. In GDM, inflammation and oxidative stress may suppress PROC

gene expression or Protein C activity[20]. In the present study, ultrasonographic evaluation was conducted in 200 women diagnosed with gestational diabetes mellitus to explore the potential etiologies of fetal growth restriction (FGR). Owing to the financial limitations associated with Doppler imaging, only 15 participants underwent this advanced assessment. Remarkably, Doppler findings revealed that placental thrombosis was the predominant underlying mechanism contributing to FGR in these cases. Our results align closely with those of Samantha et al., who investigated umbilical cord thrombosis as a critical cause of intrauterine fetal demise. In their study, 12 mothers (27.9%) consented to fetal autopsy, and all examined cases demonstrated umbilical cord thrombosis as the primary cause of death[11, 17]. Similarly, Klaritsch et al. reported comparable outcomes, identifying spontaneous umbilical artery thrombosis as a key factor leading to fetal growth restriction[21]. Collectively, these findings underscore the role of thrombotic events in the placental and umbilical vasculature as major contributors to adverse fetal outcomes in GDM pregnancies. A hypercoagulable state is associated with insulin resistance and endothelial dysfunction in GDM [12]. may promote placental or cord thrombosis, thereby compromising the fetoplacental circulation and restricting fetal growth. The present study explains that maternal lipid metabolism undergoes dynamic changes throughout pregnancy. During the initial two-thirds of gestation, fat accumulation increases, primarily driven by hyperphagia and enhanced lipogenesis. In contrast, during the final trimester, maternal fat reserves diminish due to heightened lipolytic activity and reduced lipoprotein lipase function[22, 23]. These metabolic shifts represent physiological adaptations that accommodate the growing energy demands of the developing fetus and prepare the mother for childbirth and subsequent lactation[24]. Our study also revealed significantly higher levels of total cholesterol, LDL-C, and triglycerides, along with lower HDL concentrations, in women with gestational diabetes mellitus (GDM) compared in normal pregnant women; this finding is comparable to that of a study by Khan et al. [25].

The relationship between HbA1C and lipid profiles was observed when insulin activity decreased, leading to enhanced sensitivity of hormone-sensitive lipase. This, in turn, promotes lipolysis and the subsequent release of free fatty acids and glycerol into the bloodstream. When present in excessive amounts, these free fatty acids are transported to the liver, where they undergo further metabolism into lipids [26].

In addition, our results demonstrated a statistically significant difference between GDM and normal pregnancies in terms of lipid indices (the TYG and TYG-BMI indices), as reported by Xing et al. [27]. as well as statistically significant in lipid ratio (TG/HDL-c and TC/HDL-c, which is comparable to a case-control study conducted by Xingyan et al. [28] in China with 1586 pregnant women, 741 of whom were diagnosed with GDM, which found that TG/HDL-c and TC/HDL-c were higher in GDM than in normal pregnancy. GDM is defined by a state of heightened metabolic disorder (as shown in obesity, blood pressure, and hyperlipidemia), IR, and subsequent progression of -cell dysfunction are recognized as co-dependent etiological pillars[27]. In the pursuit of inexpensive predictive tools[29], the triglyceride-glucose (TyG) index has proven to be a particularly robust biomarker. Evidence indicates that the TyG index serves as a specific proxy for muscle-centric insulin resistance and demonstrates predictive value for IR[29]. Moreover, the predictive value of the TyG index for IR has been shown to surpass that of HOMA-IR. Beyond assessing IR, the TyG index can also reflect the vulnerability of -cells to damage from high blood sugar (glucotoxicity) and excess fat (lipotoxicity). When triglycerides accumulate in the islets, they disrupt normal glucose metabolism and trigger lipolysis, which raises circulating free fatty acid (FFAs) levels and further impairs -cell function. In addition, persistent high blood sugar levels combined with reduced antioxidant defenses subject islet cells to ongoing oxidative stress, accelerating -cell failure[25]. Furthermore, in our study, we found that the TYG index and TG/HDL-C ratio early in pregnancy could help identify women at a higher risk of developing GDM. Our findings are similar to those of a study conducted in China involving 1,073 adult women with singleton pregnancies enrolled between June 2017 and September 2019 [30]. The interplay between hyperglycemia, dyslipidemia, and coagulation dysregulation likely contributes to the impairment of the placental microvasculature, thereby elucidating the increased incidence of miscarriage in affected women [31, 32]. These findings underscore the imperative for thorough biochemical surveillance, encompassing Protein C levels, during antenatal care to facilitate the early identification of pregnancies at elevated risk [32].

5. CONCLUSION

We found that insulin resistance in gestational diabetes mellitus is associated with elevated protein C levels, which may enhance hypercoagulation within the placenta, leading to restricted fetal growth and, consequently, fetal loss.

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