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Research Paper

Investigating the Relationship Between Serum C-Reactive Protein, Ferritin levels, and Gestational Diabetes in Pregnant Women Living in Qazvin City

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ABSTRACT

Background: This study aimed to compare the serum levels of C-reactive protein (CRP) and ferritin in the first trimester of pregnancy between normal and abnormal pregnant women (complicated with gestational diabetes) to determine if these chemicals have any predictive value in the diagnosis of gestational diabetes.

Methods: This prospective cohort study was carried out on 300 pregnant women attending the Prenatal Clinic of Kosar Hospital, Qazvin City, Iran, during 2017-2018. Based on Carpenter and Constant criteria, the pregnant women undertook an oral glucose tolerance test with 75 g glucose to diagnose gestational diabetes. We also measured the serum levels of CRP and ferritin in all the women in the first trimester. The obtained data were analyzed using SPSS software version 24. $P<0.05$ was considered statistically significant

Results: A total of 40 pregnant women were found to have gestational diabetes. The levels of CRP and ferritin were slightly higher in women with gestational diabetes, although this increase was not statistically significant. Regarding the receiver operating characteristic curve, body mass index (BMI) could predict the incidence of gestational diabetes (72.5% sensitivity, 53.1% specificity, $P=0.023$). The higher BMI and CRP levels in the first trimester were also significantly associated with macrosomia, which could predict macrosomia with 75% sensitivity, 73.6% specificity for BMI ($P=0.005$), and 87.5% sensitivity, 58.1% specificity for BMI.

Conclusion: There was no correlation between CRP and ferritin levels and gestational diabetes in the first trimester of pregnancy. BMI before pregnancy was the only variable related to gestational diabetes. Increased values of both CRP and BMI were associated with fetal macrosomia

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1. Introduction

Gestational diabetes mellitus (GDM) is a disorder of carbohydrate tolerance complicating pregnancy at different ages [1]. In the United Stated, gestational diabetes affects nearly 5% of pregnancies, yet the rate of its global prevalence may vary according to race, ethnicity, age, BMI, screening methods, and diagnostic criteria (ranging 1%-14%) [2]. Because of obesity and higher pregnancy ages, the incidence of gestational diabetes in Iran is higher than the average global rates [3]. The risk factors for GDM are still unknown. However, according to the literature, they could be listed as having a positive history of gestational diabetes in the patient and among immediate family members, higher pregnancy ages, obesity, hypertension, macrosomia, and glucose metabolism disorder [4]. Despite over 50 years of research, there is still considerable controversy surrounding the screening and diagnostic methods of gestational diabetes [5]. In its latest recommendations, the American College of Obstetrics and Gynecologists (ACOG) recommends applying a two-phase screening of all pregnant women. The initial screening phase is to give 50 g of oral glucose regardless of the fasting time. The sensitivity of the test depends on the selected threshold for normal values. Where<140 mg/dL is considered normal, the sensitivity is 73%-84%. While with the threshold of <135 mg/dL, the sensitivity rises to 78%-85% but specificity declines. Women with an abnormal 50 g OGCT (oral glucose challenge test) undergo an OGTT (oral glucose tolerance test) (100 g) for a definite diagnosis [6]. The American Diabetes Association (ADA), along with World Health Organization (WHO), recommends a 2-hour OGCT (OGCT2h) with 75 g of oral glucose screening for all women between the 24th and 28th weeks of pregnancy.

After delivery, GDM recovers in 90% of the patients, yet they are prone to an increased risk of type 2 diabetes and obesity throughout their lifetime [7]. GDM is associated with some pregnancy and neonatal complications such as gestational hypertension, an increased risk of cesarean delivery, fetal macrosomia, intrauterine fetal death, neonatal polycythemia, hyperbilirubinemia, hypoglycemia, and hypocalcemia. GDM may also lead to dyslipidemia and deteriorating local and systemic inflammatory responses in the body. The major pathophysiologic mechanism of GDM is insulin resistance [8], yet there is no consensus on the factors that may lead to such resistance [9], as well as the importance of the role of each factor.

Ferritin and inflammatory indexes like CRP are the factors worth investigating. CRP, an acute-phase protein and a reliable source of iron and ferritin, rises during inflammatory processes. Biological and epidemiological evidence have demonstrated that GDM may be associated with a rise in ferritin levels and the consumption of iron supplements. It has also been suggested that the excessive density of iron in the serum may cause disorders in pancreatic beta cells and glucose metabolism. As iron catalyzes the production of hydroxyl radicals from hydrogen peroxide, iron is a source of oxidative stress. As demonstrated by Rajpathak et al., [10] free radicals have a two-sided effect: when lower in value, they recover insulin sensitivity, whereas an increase in their value strongly correlates with hyperglycemia. This finding is also supported by the low frequency of after-feeding hyperinsulinemia in those who regularly donate blood and subsequently suffer from iron-deficiency anemia [10]. Researchers have demonstrated that ferritin levels are high in pregnant women with GDM, yet it has not been determined whether the rise is an index of inflammation or a growing concentration of iron [11]. CRP is a highly-detectable protein during the acute phases of diseases, undergoing an upsurge in response to inflammation.

It is assumed that CRP plays a role in GDM. The molecular basis of the association between infection and diabetes is attributed to the reactions of the cytokines like interleukin-6 and tumor necrosis factor. Such inflammatory factors are antagonists to insulin, raising the tolerance to insulin and stimulating acute inflammatory responses [8, 12]. The significance of the disease and its high prevalence in our country, limited studies in this regard, and conflicting results of present studies made us investigate the relationship between CRP/ferritin and GDM incidence.

2. Material and Methods

This prospective observational study was performed on 300 healthy pregnant women aged 18-40 years. The study sample was selected by a convenience sampling method. They had a singleton pregnancy and entered the study before the 16th week of pregnancy. The demographic information, including age, parity, body mass index (BMI), and a history of diabetes in the participant or the immediate family, was recorded on a checklist. There were also questions concerning the consumption of iron pills and the dosage during or before pregnancy. All patients underwent a sonographic examination to exclude multiple gestations. All participants were referred to a single laboratory to have their levels of CRP and ferritin measured before the 16th week of pregnancy.

Their pre-pregnancy BMI was also calculated based on height and weight before pregnancy.

This value was used to classify into four groups: low, normal, overweight, and obese. A glucose tolerance test (GTT of 75g) was run to diagnose diabetes between 24 and 28 weeks of gestation. Those with one of the following criteria were considered to have GDM: fasting blood sugar ≥92 mg/dL, OGTT1h ≥180 mg/dL, or OGTT2h ≥153 mg/dL. Using these diagnostic criteria, 40 women were diagnosed with gestational diabetes. All patients were followed until delivery; the infants' weight was recorded before the data analysis. The inclusion criteria were as follows: women aged 18 to 40 years and singleton pregnancy between 12 and 16 weeks. The patients with the following conditions were excluded from the study: having diabetes before pregnancy, thalassemia, fetal or uterine anomalies, chronic inflammatory disorders like Crohn's and ulcerative colitis, intrauterine fetal death during the current pregnancy, hypothyroidism, recent bacterial or viral infections (less than 30 days), and autoimmune diseases. The study enjoyed convenient sampling.

A sample size of 300 patients was determined to address error type I of 0.05 and error type II of 0.01. The SPSS software version 24 was employed for statistical analysis and calculating the mean and standard deviation for the quantitative variables and frequency for the qualitative ones. The Chi-square and Fischer tests, along with the Student t test and Mann-Whitney test, were used to compare the levels of GDM incidence among those with normal and high concentrations of CRP and ferritin (P<0.05). A receiver operating characteristic curve was plotted to estimate the sensitivity and specificity. The area under the curve was also calculated (Figures 1 and 2).

3. Results

The incidence of GDM was 13.33% in our samples. The ratio of patients with a positive family history of diabetes among the patients with GDM was 22.5% compared to the healthy participants (14.23%). However, the difference was not statistically significant (P=0.13). As regards BMI, 65% of those suffering from GDM were overweight (52.5%) or obese (12.5%), while the figure was 44.22% in the healthy cases (8.84% obese and 35.38% overweight). Also, 55.78% of healthy participants had normal (53.85%) or low weight (1.92%,) whereas this figure was 35% among patients suffering from GDM. The difference was found to be statistically significant (P=0.024). About 70% of all cases with GDM were multiparous, and the remaining 30% were nulliparous (statistically significant, P<0.001). The incidence of macrosomia was found to be 7.5% in patients with GDM and 5% in non-GDM cases, and the difference was not significant (P=0.367) (Table 1).

According to Table 2, BMI was the only variable found to be significantly different in the groups (26.12% compared to 24.82%, P=0.023). Table 3 indicates that BMI is the only variable that can predict the probability of GDM in the patient (P=0.023, area under curve [AUC]=0.612).

Among the variables, CRP and BMI before pregnancy had a significant difference in pregnancies with or without fetal macrosomia, i.e., pregnancies complicated with fetal macrosomia correlated with higher levels of CRP (11.25% compared to 7.75%, P=0.46) and BMI (27.25% compared to 24.87, P=0.006). Referring to Table 4, CRP (AUC=0.718, P=0.003) and BMI (AUC=0.707, P=0.005) had positive predictive value for the incidence of fetal macrosomia.

4. Discussion

The present observational study aimed to investigate how the CRP and ferritin levels in the first trimester of pregnancy may be associated with the GDM incidence in 300 healthy pregnant women. During the first trimester, CRP levels reached the mean value of 8.6 mg/L in the GDM group in contrast to 7.6 mg/L in the non-GDM group, and the mean levels of ferritin were 43.27 and 40.38 in the same order.

Although the levels of CRP and ferritin were higher among those with GDM than among healthy women, the difference was not statistically significant (P=0.597 and P=0.375). The sensitivity and specificity of CRP in the diagnosis of GDM were 57.5% and 53.1%, and those related to Ferritin were 65% and 43.5%. The study also found that among CRP, BMI, fasting blood sugar (FBS), OGTT1h and OGTT2h, ferritin, and age, only CRP (mean of 11.25 compared to 7.75) and BMI (mean of 27.35 compared to 24.87) correlated with macrosomia (P=0.046 and P=0.006). In this study, the rate of GDM in the sample was estimated to be 13.33% which was within the global range reported by the literature (1%-14%), yet it was higher than that of the domestic GDM rate (2.8%-3.6%) as found in the local studies. In agreement with our results, Ozgu-Erdint et al. studied a sample of 439 pregnant women, finding a GDM frequency of 11.2% [13].

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Table 1. Distribution of quantitative and qualitative variables before the study in pregnant women

Demographic Characteristics		Mean±SD/No. (%)
Age (y)		29.13±9.72
BMI (kg/m^2)		25.36±3
Ferritin (ng/mL)		40.87±36.72
CRP (mg/L)		7.93±6.84
Infant weight (g)		3330.42±432.83
Gestational age (wk)		12.72±0.77
GDM due to pregnancy	Yes	40(13.3)
	No	260 (86.7)
Parity	Nulliparous	161(83.7)
	Multiparous	139(46.3)
BMI before pregnancy	Low weight	5(1.7)
	Normal weight	154(51.3)
	Overweight	113(37.3)
	Obese	28(9.7)
Family history of GDM	Yes	46(15.3)
	No	254(84.7)
Macrosomia	Yes	16(5.3)
	No	284(94.7)

GDM: gestational diabetes mellitus; BMI: body mass index; CRP: C-reactive protein.

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Table 2. Comparing study variables in GDM and Non-GDM groups

Variables	Mean±SD		P
	GDM (n=40)	Non-GDM (n=260)	
Ferritin (ng/mL)	43.03±27.13	40.44±38.01	0.597
CRP (mg/L)	8.83±6.52	7.79±6.89	0.375
Age (y)	31±5.26	29.73±14.59	0.589
BMI (kg/m$^{2)}$	26.12±3.12	24.82±3.36	0.023
Gestational age (wk)	12.80±0.80	12.71±0.76	0.507
Infant weight (g)	3404±534.67	3316.93±414.18	0.248

GDM: gestational diabetes mellitus; BMI: body mass index; CRP: C-reactive protein.

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Table 3. Sensitivity and specificity of CRP, Ferritin, and BMI before pregnancy in predicting GDM incidence

Variable	Sensitivity	Specificity	AUC	Cut-Off Point	P
BMI	72.5%	53.1%	0.612	24.3	0.023

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GDM: gestational diabetes mellitus; BMI: body mass index; CRP: C-reactive protein; AUC: the area under curve.

Table 4. Sensitivity and specificity of C-Reactive Protein (CRP), Ferritin, and Body Mass Index (BMI) before pregnancy in predicating macrosomia incidence

Variables	Sensitivity (%)	Specificity (%)	AUC	Cut-off Point	P
Ferritin	68.8	29.6	0.495	22.5	0.954
CRP	87.5	58.1	0.718	7.5	0.003
BMI	75	73.6	0.707	26.85	0.005

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In agreement with the results of our study, Syngelaki et al. worked on a sample of 1000 women (200 with GDM and 800 without GDM) and found no significant difference between the two groups in their levels of high sensitivity CRP (hs-CRP) during the first trimester (P=0.084) [14]. They also examined the ROC to show that when coupled with hs-CRP, maternal factors did not have any predictive value of GDM incidence (AUC=0.822, P=0.219), which was the same in our study.

Measuring kits of hs-CRP have been widely accessible during recent decades. The kits apply highly sensitive techniques like ELIZA, resonant acoustic profiling, and immunoturbidimetry to identify even inconsiderable levels of CRP (0.01-10 mg/L) and small degrees of inflammation in the absence of apparent inflammatory and immune disorders. The kits, therefore, make hs-CRP a better choice to diagnose lower degrees of systemic inflammation in the cases of insulin resistance and GDM [15]. Zhao et al. selected weeks 24-28 to investigate a sample of 102 patients (32 normal pregnant women, 41 women with glucose intolerance, and 29 women with GDM) [16].

Ozgu-Erdint et al. measured the levels of hs-CRP between 11 and 13 weeks of gestation to examine their relationship to GDM. The authors recorded a sensitivity of 87.2% for hs-CRP in the diagnosis of GDM [13], which was higher than what we found. The difference could be explained by the fact that they focused on hs-CRP rather than CRP.

Table 5. Comparing study variables in Macrosomia and Non-Macrosomia groups

Variables	Mean±SD		P
	Macrosomia (n=16)	Non-Macrosomia (n=284)	
Ferritin (ng/mL)	42.0±31.10	40.72±37.10	0.892
CRP (mg/L)	11.25±4.25	7.75±6.90	0.046
Age (y)	28.43±3.96	29.98±14.07	0.661
BMI (kg/m^2)	27.25±3.35	24.87±3.32	0.006
Gestational age (wk)	13.54±1.07	12.67±0.72	0.006
Infant weight (g)	4185.0±108.56	3280.29±391.01	<0.001

GDM: gestational diabetes mellitus; BMI: body mass index; CRP: C-reactive protein.

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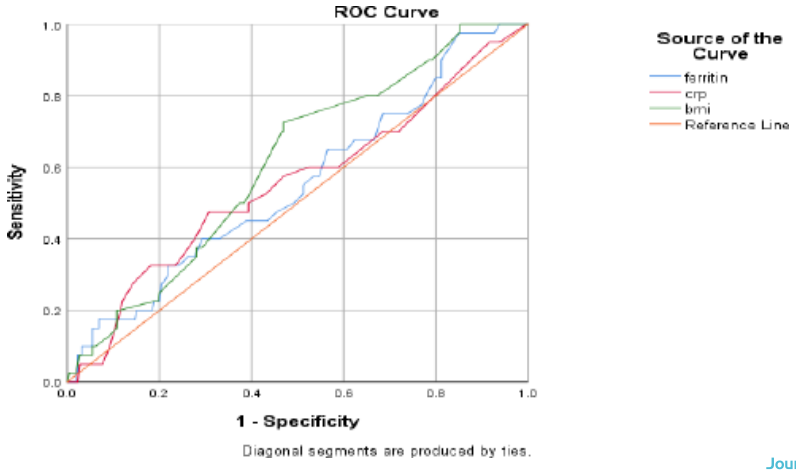

Figure 1. Receiver operating characteristic curve of C-Reactive Protein (CRP), Ferritin, and Body Mass Index (BMI) in predicting gestational diabetes mellitus incidence

Similarly, Zhao et al. estimated the GDM frequency to be 11.6%. They examined the levels of CRP and ferritin at the first prenatal visit (before the 16th week of pregnancy) and used OGTT (75g) to investigate if the levels had any correlation to GDM between 24 and 28 weeks of pregnancy [16]. The results of their study indicated that CRP and ferritin levels did not significantly correlate with GDM during the first trimester of pregnancy (P=0.597, P=0.357) [16]. The sensitivity and specificity of CRP in the diagnosis of GDM were 57.5% and 53.1%, respectively. Ferritin had a sensitivity of 65% and a specificity of 43.5%. In contrast to the results of the present study, they concluded that hs-CRP, interleukin (IL)-6, and IL-8 were significantly higher in the patients with GDM and glucose intolerance [16]. The discrepancy may result from the difference in gestational age and the factors under investigation (hs-CRP vs CRP in our work).

In 2003, Wolf et al. studied 43 pregnant women with GDM and 94 normal cases [17]. Contrary to our results, they found that during the first trimester, CRP levels were significantly higher in the patients with GDM (P<0.001). The difference was probably due

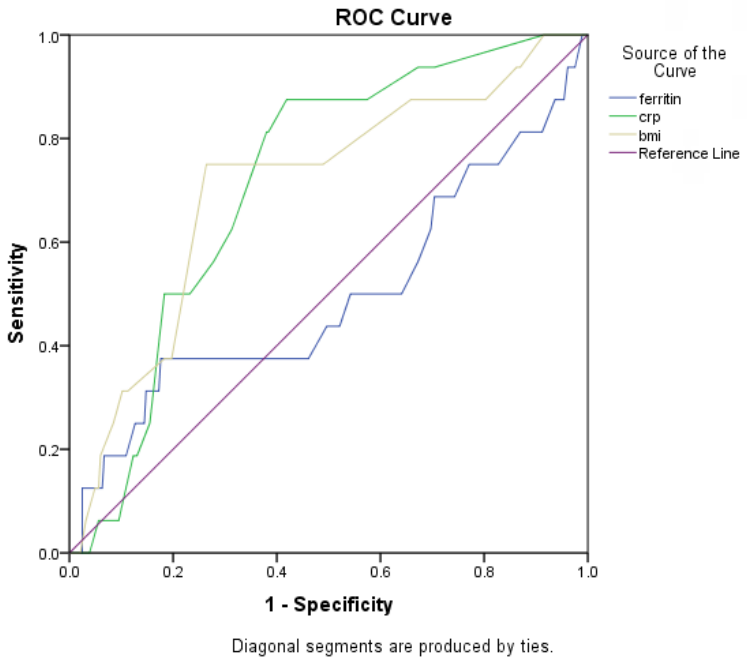

Figure 2. Receiver operating characteristic curve of C-reactive protein, ferritin, and body mass index in predicting macrosomia incidence

to the different sample sizes and higher frequency of GDM in their study [17].

In 2016, Bowers et al. [18] compared 350 pregnant women with GDM and 349 healthy pregnant women, observing that during the first trimester, the levels of ferritin and transferrin saturation were significantly higher in the GDM group. The sample size and frequency of GDM might well explain the difference between their results and the findings of our study. Amiri et al. worked with two equal-size groups (100, 64, and 34 women in each group). They measured ferritin levels during the first trimester of pregnancy and checked for possible relationships with GDM [3]. In contrast with our results, they all found higher levels of ferritin, probably owing to the difference in measurement timing and equality of the sample size in both groups.

Based on the present study, among CRP, BMI, FBS, OGTT1h, OGTT2h, and age, only CRP (P=0.046) and BMI (P=0.006) were associated with macrosomia. The variables mentioned above were higher in those with fetal macrosomia and ferritin (42 compared to 40.72) (Table 5).

5. Conclusion

The results of the present study show that although the levels of CRP and ferritin during the first trimester were higher in the women with GDM, the figures were not statistically significant, and the proteins had little predictive value in diagnosing GDM. CRP levels, however, were independently associated with macrosomia during the first trimester of pregnancy and may be used as a predictive factor in this regard. BMI before pregnancy had a positive relationship with GDM and macrosomia; that is, women with higher BMI were more likely to develop GDM and have a baby with macrosomia.

Study Suggestions

Because of the high incidence of GDM and its complications and the significance of finding factors to predict the disease, further studies are recommended to be conducted in a larger sample size. On the other hand, hs-CRP can be a more sensitive marker than CRP in diagnosing systemic inflammation, allowing early and precise prediction of the disorder so that preventive interventions and other supervision could be well performed from early pregnancy. As in this study, the frequency of GDM was higher than in other local studies; further GDM studies may be necessary to evaluate the factors influencing GDM incidence and develop preventive measures.

Ethical Considerations

Compliance with ethical guidelines

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Authors' contributions

Conceptualization and Supervision: Fatemeh Lalooha and Khadijeh Elmizadeh; Methodology: Farideh Movahed; Investigation, Writing-original draft, and Writing-review & editing: All authors; Data collection: Sania Rahimi, Fatemeh Lalooha, and Venus Chegini; Data analysis: Fatemeh Lalooha and Khadijeh Elmizadeh; Funding acquisition and Resources: Farideh Movahed.

Conflict of interest

The authors declared no conflict of interest regarding the publication of this article.

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