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ORIGINAL ARTICLE

Prediction of Gestational Diabetes Mellitus in The First Trimester: comparison of maternal fetuin-A, N-terminal pro-atrial natriuretic peptide, high-sensitivity C-reactive protein, and fasting glucose levels

Saz Abdulateef Jabali [1,*] and Khalidah Amin [2]

[1]*Department of Obstetrics and Gynecology, Shahid Hoshang Hospital, Sulaimaniyah, IRAQ.*
[2]*Department of Obstetrics and Gynecology, College of Medicine, University of Kirkuk, Kirkuk, IRAQ.*

[*]*Corresponding author email: hantoos5soozy@gmail.com*

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy. This study aims to evaluate the diagnostic value of first trimester maternal fetuin-A, N-terminal pro atrial natriuretic peptide (pro-ANP), high-sensitivity C-reactive protein (hs-CRP), and fasting plasma glucose (FPG) in the prediction of GDM.
Methods: Over 10 months ending in December 2020, 88 low-risk pregnant women attending routine antenatal care in Hawler Maternity Hospital, Erbil, Iraq were enrolled. Maternal venous blood samples were collected for futin-A, pro-ANP, hs-CRP, and FPG. Glucose challenge test (GCT) and oral glucose tolerance test (OGTT) were performed for those with high FPG level.
Results: Six of 88 (6.8%) women developed GDM. There was no statistically significant difference between GDM and non-diabetics groups regarding age, gravidity, parity, early pregnancy BMI, and gestational age. There was no significant difference between the 2 groups regarding N-terminal pro-ANP levels but FPG and hs-CRP levels were higher and futin-A levels were lower in the GDM group.
Conclusion: The utility of maternal serum hs-CRP, Fetuin-A, and FPG levels as simple-to-do reliable tests to predict the development of GDM.

Key words: Gestational diabetes mellitus; hs-CRP; Maternal fetuin-A; N-terminal pro atrial natriuretic peptide.

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy, between 1-20% of pregnancies could be complicated by GDM depending on the studied population and the diagnostic criteria employed. The prevalence of the disease is increasing due to the modern lifestyle [1].

GDM is formally defined as a condition in which carbohydrate intolerance develops during pregnancy. Normally, insulin resistance may be increased, decreased, or remain unchanged during the first trimester of pregnancy [2]. In contrast, insulin resistance rises by 40–60% during the 2nd and 3rd trimesters of pregnancy to ensure proper glucose supply to the fetus. This is associated with a compensatory increase in insulin production and/or secretion to maintain glucose homeostasis [3]. In GDM, glucose intolerance occurs most likely due to decreased insulin sensitivity, without the ability to compensate by increasing insulin secretion. Hence, GDM can result from numerous changes in the metabolism of pregnant women [4].

GDM is a heterogeneous disease process whose exact etiology and pathogenesis are not clear [5]. Most diagnoses of GDM are made in the late 2nd or early 3rd trimesters of pregnancy [3] using the guidelines of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in which an oral glucose tolerance test (OGTT) is performed between the 24th and 28th weeks of gestation. However, diagnosis of GDM at this period of pregnancy may be late and could lead to short- and long-term consequences for the child and his/her mother. Therefore, earlier detection of GDM is desired as it permits earlier prevention and treatment of the disease [4].

GDM is associated with significant risks for both the mother and the offspring. Therefore, the American Congress of Obstetricians and Gynecologists (ACOG) recommends early screening for GDM in women with risk factors such as a body mass index (BMI) >25 kg/m2, hypertension, known impaired glucose metabolism, and family history of diabetes. The identification of early pregnancy biomarkers, readily obtained from blood samples, may complement existing clinical risk factors in detecting women at high risk of developing GDM [6].

Many authors found that fasting plasma glucose (FPG) concentration is more accurate than traditional risk factors, such as BMI or age, in the prediction of GDM [7]. In a study that involved 2116 pregnant women, fasting glucose concentration > 4.5 mmol/L during the first trimester offered optimal sensitivity and specificity for GDM prediction [8]. As the inflammatory response is enhanced in GDM, inflammatory markers are probably involved in the development of GDM and could be used as predictive markers. The C-reactive protein (CRP) and the high sensitivity-CRP (hs-CRP) are inflammatory markers which are increased in GDM and particularly during the first trimester of gestation [4].

Fetuin-A is a newly identified biomarker primarily secreted by the liver and adipose tissue and is linked to insulin resistance and metabolic syndrome [9]. Its mechanism involves inhibiting the insulin receptor, thereby increasing insulin resistance. Moreover, it has a protective or anti-inflammatory effect and is considered a negative acute phase reactant (AFR). Several prior studies have investigated the relationship between fetuin-A levels and markers of insulin resistance during uncomplicated pregnancies or those complicated by GDM [10].

Atrial natriuretic peptide (ANP) is a peptide hormone mainly secreted by the heart, circulating as a prohormone (pro-ANP). Several studies have observed a relationship between plasma glucose, insulin, and ANP levels. A rapid increase in ANP levels occurs in response to acute hyperglycemia [11].

Prior research has demonstrated that decreased fetuin-A, increased high-sensitivity C-reactive protein (hs-CRP), and fasting plasma glucose (FPG) levels in women during the first trimester may serve as potential biomarkers for the early identification of GDM [12, 13].

This study aims to assess the diagnostic utility of first trimester fetuin-A, pro-ANP, hs-CRP and FPG levels in predicting GDM among a cohort of pregnant women in Erbil, Iraq.

MATERIAL AND METHODS

This prospective study was conducted in the Department of Obstetrics and Gynecology, Hawler Maternity Teaching Hospital, Erbil, Iraq over the 10 months ending on December 2020. The study protocol was ethically approved and Verbal consents were obtained from all cases who attended routine antenatal care and agreed to participate in the study.

During the initial antenatal visit in the first trimester, medical history and demographic characteristics, including maternal age and parity, early pregnancy BMI, past medical (including history of polycystic ovarian syndrome [PCOS]) and obstetrical history, family history of DM in a first-degree relative, previous history of macrosomic baby (>4.5 kg) were noted as well as smoking, drug history, occupation and type of diet. All participants consumed a Mediterranean diet and were of the same nationality.

Women were excluded from the study in the presence of one or more of the following:

- Age below 18 or above 40.
- Pre-existing diabetes, and hypertension.
- Thyroid dysfunction.
- Uncontrolled endocrine disorders.
- Abnormal renal function.
- FPG levels exceeding 126 mg/dl.
- Parity above 4.
- Early pregnancy BMI >30 kg/m2.
- Previous history of PCOS.
- Previous history of macrosomic baby.
- Family history of DM in a first-degree relative.
- Smoking and chronic use of drugs.

Eligible candidates had a clinical assessment of the fundal height and ultrasonic confirmation of gestational age at 11-14 weeks. Moreover, the BMI was calculated by dividing the weight (kg) by the height (m^2). According to the WHO Classification, women were considered underweight (BMI<19.9), normal weight (BMI=20–24.9), overweight (BMI=25–29.9), mildly obese [class I] (BMI=30–34.9), moderately obese [class II] (BMI=35–39.9), and morbidly obese [class III] (BMI>40) [14]. A complete blood count, thyroid function tests, and midstream urine analysis were performed as part of the routine antenatal check.

Additionally, venous blood samples were collected for the measurement of fetuin-A, pro-ANP, hs-CRP, and FPG. The maternal blood samples were immediately centrifuged, and the serum was separated and stored at -80°C for subsequent analysis. The levels of fetuin-A, pro-ANP, and hs-CRP were measured and quantified using enzyme-linked immunosorbent assay (ELISA) kits. (YEHUA Biological Technology, Shanghai, China) at eleven to fourteen weeks of gestation. Maternal blood samples were immediately centrifuged, and the serum was separated and stored at −80 °C for further analyses. FPG levels were measured using the OK Biotech Co. Ltd glucometer 4F-1, No. 83, Sec. 2, Hsinchu City, Taiwan. All results were documented accurately, and candidates were asked to schedule a follow-up appointment at 24 weeks of gestation.

In the second trimester visit (between the 24th and 28th weeks of gestation), all subjects were screened for GDM. The patient was instructed to drink a 50 g glucose solution for the Glucose Challenge Test. After one hour, the blood sugar level was measured. A blood sugar level of less than 140 mg/dl (7.8 mmol/L) was considered normal. A higher level indicated the need for an OGTT. For the Oral Glucose Tolerance Test, the patient was required to fast overnight, followed by measuring the blood sugar level two hours after consuming a 75 g glucose solution. GDM would be diagnosed if the FPG was greater than 100 mg/dl and the 2-hour blood glucose level exceeded 140 mg/dl.

For statistical analysis, the software package for Social Sciences (SPSS), version 21 was utilized. The G*Power v.3.1.5 general power analysis program was employed for sample size calculations. Categorical variables were presented as frequencies and percentages, whereas continuous variables were summarized using means and standard deviations (SD). Independent samples t-tests were employed to compare continuous variables with normal distribution. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were determined for each method. The predictive accuracy of [variables/models] for GDM was assessed using receiver operating characteristic (ROC) curve analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among 88 women who completed antenatal follow-up, 6 (6.8%) developed GDM. The demographics and obstetrical variables are shown in Table 1.

Youden's index was utilized to determine the cutoff value for diagnosing GDM. A two-tailed P-value <0.05 was deemed statistically significant. There was no statistically significant difference between the two groups regarding age, gravidity, parity, early pregnancy BMI, and gestational age. Table 2 compares the levels of maternal fetuin-A, pro-ANP, hs-CRP, and FPG between the two groups.

In GDM cases compared to healthy (non-diabetic) pregnant women, hs-CRP levels were significantly higher, measuring 8.81 ng/ml (3.54-27.9) versus 4.93 ng/ml (3.18-24.5), respectively, with a P-value of 0.005. Meanwhile, fetuin-A levels were significantly lower in cases complicated by GDM compared to healthy cases, with levels of 184 ng/ml (49-2787) versus 213 ng/ml (49-1863), respectively, and a P-value of 0.017.

On the other hand, there was no statistically significant difference between the two groups regarding NT pro-ANP levels (P=0.174); therefore, it was excluded from the analysis. Figure 1 shows the area under the receiver operating characteristic (ROC) curves for fetuin-A, hs-CRP, and FPG in predicting and diagnosing GDM.

The area under the ROC curves for diagnosing GDM was 0.337 (95% CI: 0.212-0.461, p = 0.017) for fetuin-A, 0.702 (95% CI: 0.592-0.812, p = 0.005) for hs-CRP, and 0.738 (95% CI: 0.626-0.850, p < 0.004) for FPG, respectively.

Table 1. Demographic and Obstetrical Characteristics of the Study Population

Variable	GDM Group (n=6)	Non-GDM Group (n=82)	p-value
Age (years), Mean ± SD	29.8 ± 4.0	29.7 ± 3.3	0.111
Gravidity, Median (Range)	3 (1–4)	2 (1–4)	0.129
Parity, Median (Range)	1 (0–3)	1 (0–3)	0.110
Gestational Age (weeks + days)	11+1 (11+0 – 13+6)	11+2 (11+0 – 13+6)	0.120
Early Pregnancy BMI, Mean ± SD	27.1 ± 2.7	27.2 ± 2.4	0.646

GDM = Gestational Diabetes Mellitus.

Table 2. Comparison of First-Trimester Biomarker Levels Between the Study Groups

Biomarker	GDM Group (n=6)	Non-GDM Group (n=82)	p-value
Fetuin-A (ng/mL), Median (Range)	184 (49–2787)	213 (49–1863)	**0.017**
NT-proANP (mg/dL), Median (Range)	697 (464–4997)	725 (484–4581)	0.174
hs-CRP (ng/mL), Median (Range)	8.81 (3.54–27.9)	4.93 (3.18–24.5)	**0.005**
FPG (mg/dL), Mean ± SD	92.9 ± 7.9	85.7 ± 8.2	**<0.004**

GDM = Gestational Diabetes Mellitus; NT-proANP = N-terminal pro-atrial natriuretic peptide; hs-CRP = High-sensitivity C-reactive protein; FPG = Fasting plasma glucose.

Maternal hs-CRP levels above 4.65 ng/ml exhibited the highest sensitivity (85.21%, 95% CI: 67.48-95.48), NPV (89.24%, 95% CI: 76.61–98.16), and PLR (61.46%, 95% CI: 50.34-71.48), with a diagnostic accuracy of 89.64%. Fetuin-A levels below 166 ng/ml demonstrated the highest specificity (77.27%, 95% CI: 67.11-87.98), NLR (65.87, 95% CI: 54.78-77.65), and PPV (64.84%, 95% CI: 36.31-72.52), with a diagnostic accuracy of 71.45%. FPG levels above 88.5 mg/dL had a sensitivity of 77.31% (95% CI: 59.64-91.39), specificity of 58.32% (95% CI: 46.76-72.67), and the PPV and NPV were 47.94% (95% CI: 34.73-64.74) and 86.37% (95% CI: 70.34-93.81), respectively, with a diagnostic accuracy of 86.23%, as detailed in Table 3.

Table 3. Diagnostic Performance of First-Trimester Biomarkers (FPG, hs-CRP, and Fetuin-A)

Index	FPG	hs-CRP	Fetuin-A
Cut-off value	88.5 mg/dL	4.65 ng/mL	166 ng/mL
Sensitivity (%), 95% CI	77.3 (59.6–91.4)	85.2 (67.5–95.5)	59.6 (38.1–76.9)
Specificity (%), 95% CI	58.3 (46.8–72.7)	50.9 (37.6–64.0)	77.3 (67.1–88.0)
Positive Likelihood Ratio, 95% CI	1.85 (1.39–2.46)	1.73 (1.28–2.34)	2.63 (1.57–4.40)
Negative Likelihood Ratio, 95% CI	0.39 (0.17–0.88)	0.29 (0.11–0.76)	0.52 (0.31–0.86)
Positive Predictive Value (%), 95% CI	47.9 (34.7–64.7)	49.3 (32.8–60.3)	64.8 (36.3–72.5)
Negative Predictive Value (%), 95% CI	86.4 (70.3–93.8)	89.2 (76.6–98.2)	75.9 (67.8–89.2)
Diagnostic Odds Ratio, 95% CI	5.79 (1.98–16.78)	6.87 (2.00–22.88)	4.65 (1.76–13.80)
Diagnostic Accuracy (%)	86.2	89.6	71.5

FPG = Fasting Plasma Glucose; hs-CRP = High-Sensitivity C-Reactive Protein; CI = Confidence Interval.

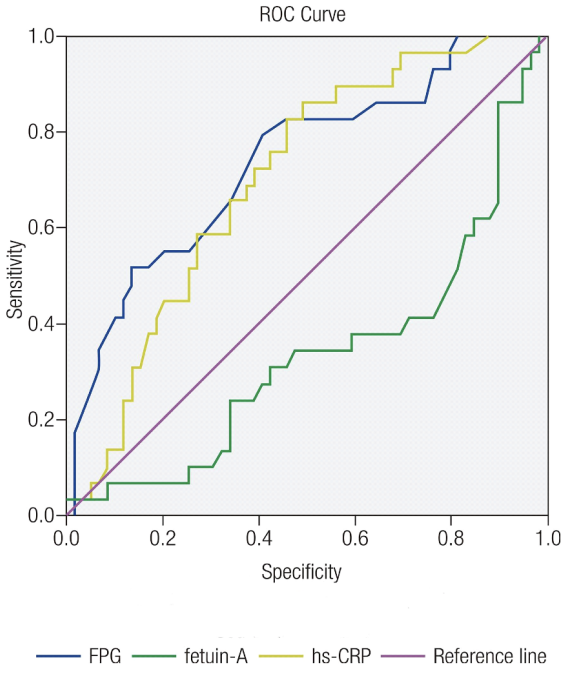

Figure 1. Area under the receiver operating characteristic (ROC) curves for fetuin-A, hs-CRP, and FPG in predicting GDM.

DISCUSSION

Gestational diabetes mellitus can lead to adverse outcomes for mothers and fetuses, including both immediate and long-term complications. For early recognition of GDM, many validated prediction models have been developed. In this study, the levels of diagnostic value of fetuin A, pro-ANP, and hs-CRP in the first trimester were evaluated to predict GDM. High levels of hs-CRP and low levels of fetuin-A at 11 to 14 weeks of gestation were associated with GDM later in pregnancy by inverse correlation.

Of all pregnancies, GDM affects 4-6% of pregnancies and is a leading cause of maternal and neonatal morbidity and mortality, primarily due to delayed recognition of impaired glucose tolerance during the second or third trimester. Poor glycemic control during pregnancy is associated with increased risks of miscarriage, preterm birth, stillbirth, macrosomia, urinary tract infections, polyhydramnios, shoulder dystocia, operative delivery, neonatal hyperbilirubinemia-hypocalcemia, and NICU admission. Therefore, achieving good glycemic control is the cornerstone of GDM management. Therefore, to help predict this complication and improve the management of these cases, some first-trimester markers may help [15].

Fetuin-A is a glycoprotein produced primarily by hepatocytes and is involved in a diverse range of physiological and pathological conditions. It has been associated with insulin signaling pathways and may be involved in the development of insulin resistance and type 2 diabetes. GDM is characterized by elevated insulin resistance and impaired glucose tolerance in the second half of pregnancy. It has been associated with elevated maternal circulating fetuin-A levels in some but not all studies [9].

In patients with type 2 DM, studies have reported high levels of fetuin-A, while in other studies the levels were low and therefore, the results have been controversial and limited. Kalabay et al. [16] and Iyidir et al. [17] Stated that increased levels of fetuin-A in women with GDM compared to healthy pregnant women in second to third trimester gestational weeks, whereas Farhan and cols. Farhan S et al. [18] observed no differences in fetuin-A levels in the third trimester of pregnancy and in the postpartum period in a group patients with GDM. The study of Briana et al. [19] was done in the second and third trimesters of pregnancy, as well as during labour period and at the postpartum periods, so there were no suffi-

cient data evaluating the levels of maternal fetuin-A levels at eleven- fourteen weeks of gestation for predicting GDM.
This study revealed that fetuin-A concentrations were significantly lower in women with gestational diabetes mellitus (GDM) compared to healthy pregnant women. This decrease in fetuin-A levels may be attributed to several underlying mechanisms:

i. Inflammation-related mechanisms: Research has shown that low fetuin-A levels are associated with vascular calcifications and inflammation, whereas high levels are linked to metabolic syndrome and dyslipidemia. During early pregnancy, subclinical inflammation may contribute to decreased fetuin-A concentrations, as fetuin-A acts as a negative acute phase reactant (APR), exerting protective effects
ii. Insulin sensitivity related: The first trimester of pregnancy is known as the insulin-sensitive period. Insulin resistance has been reported to increase gradually as pregnancy progresses, especially during the second trimester.

There was no correlation found between fetuin-A levels and FPG levels. Notably, FPG levels were significantly higher in patients who subsequently developed GDM. Regarding NT pro-ANP, in this study, levels were lower in women with GDM compared to healthy pregnant women, but the difference was so small that it was not statistically significant. An inverse correlation between NT pro-ANP and metabolic syndrome, insulin resistance, and FPG were demonstrated in several cross sectional studies such as that of Magnusson et al. [20] as low NT pro-ANP concentrations predict later development of diabetes. Yuksel et al. [21] found that patients with GDM beyond 26 weeks of gestation exhibited significantly lower levels of NT-pro-ANP and displayed altered parameters of insulin resistance due to either decreased cardiac production of NT pro-ANP or increased clearance in subsequent gestational weeks. The high-sensitivity CRP level is one of the markers used to predict GDM in the early stages of pregnancy, with high specificity and a diagnostic odds ratio and has been associated with an increased risk of developing GDM. An independent risk factor for developing GDM is increased inflammation to which high values of hs-CRP are indicative. A positive association between hs-CRP levels and GDM prediction is demonstrated, as hs-CRP is a positive acute phase reactant. As fetuin-A is a negative APR, levels were significantly lower in women with GDM than in healthy pregnant women; therefore, an inverse correlation between fetuin-A and hs- CRP levels was demonstrated in maternal serum. The findings of our study were consistent with the literature, as we demonstrated that hs-CRP had better diagnostic accuracy for GDM than fetuin-A and FPG (89.64 vs 71.45 and 86.23%, respectively). Furthermore, we detected higher levels of FDG in the first trimester among women who later developed GDM similar to previous studies [22, 23]. We found similar rates of sensitivity (77.31%) and specificity (59.32%). FPG is an easier test to do and less costly to determine with a high validity comparable to that of hs-CRP. However, further research and larger-scale studies are necessary to validate these biomarkers as reliable screening tools for GDM.

CONCLUSION

The advantage of pregnant serum hs-CRP, Fetuin-A, and fasting glucose levels as simple, reliable tests to predict the development of GDM. Early screening for GDM in the first trimester permits the implementation of proper prevention and treatment.

ETHICAL DECLARATIONS

- **Ethics Approval and Consent to Participate**

  The study protocol was ethically approved by the Iraqi Board for Medical Specializations, the Scientific Council of Obstetrics and Gynecology, and the Hawler Health Directorate. Verbal consents were obtained from all cases who attended routine antenatal care and agreed to participate in the study.

- **Consent for Publication**

  Non.

- **Availability of Data and Material**

  The datasets are available from the corresponding author upon reasonable request.

- **Competing Interests**

  The authors declare that there is no conflict of interest.

- **Funding**

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- **Authors' Contributions**

All authors contributed significantly, directly, and intellectually to the work and consented to its publication.

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