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Research Article

Can First Trimester Plasma Protein A Level Predict Gestational Diabetes Mellitus

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Abstract

Aim: Gestational diabetes mellitus (GDM), a condition with multifactorial etiology and adverse perinatal consequences, affects approximately 15% of pregnancies globally, with higher prevalence in certain populations, such as Türkiye. The role of pregnancy-associated plasma protein-A (PAPP-A) on GDM risk remains unclear. This prospective study aimed to assess whether first-trimester maternal PAPP-A levels are predictive of GDM.
Material and Method: This study involved 573 singleton pregnancies in women aged 18 to 45 years, conducted at a tertiary maternity hospital. PAPP-A and free β-hCG were assessed, and GDM screening was carried out using a 75 g oral glucose tolerance test. Comprehensive statistical analyses were applied to evaluate the findings.
Results: Of the participants, 28.09% were diagnosed with GDM. GDM group exhibited significantly lower PAPP-A MoM levels compared to controls (p=0.042). ROC analysis revealed limited predictive utility, with a PAPP-A threshold of 0.99 demonstrating 52.3% sensitivity and 51.7% specificity. Logistic regression identified low PAPP-A levels, advanced maternal age, and higher body mass index (BMI) as independent GDM risk factors.
Conclusion: While the findings underscore a potential association between PAPP-A levels and GDM, the predictive capacity of PAPP-A alone is modest. Future research should explore integrated predictive models incorporating PAPP-A and other biomarkers for improved early GDM screening.

Keywords: Gestational diabetes, pregnancy-associated plasma protein-A, pregnancy

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition characterized by impaired glucose metabolism first recognized during pregnancy and diagnosed within the gestational period (1,2) and complicates approximately 15% of all pregnancies (3). The prevalence of GDM varies significantly across different countries, with studies in Türkiye indicating a high prevalence rate of 27.9%, which surpasses the rates observed in many other nations (4-6). Given the direct relationship between maternal exposure to GDM and both long/short-term adverse outcomes in offspring, it is crucial to assess the accuracy of any diagnostics, using routine first or second trimester maternal biomarkers, to identify women at risk of GDM (7).

The etiology of GDM is considered to be multifactorial (1). In the pathogenesis of GDM, the role of Pregnancy Associated Plasma Protein-A (PAPP-A) has not been fully elucidated (1,8). PAPP-A is a biomarker utilized during first-trimester screening to assess the risk of fetal aneuploidies such as Down syndrome (trisomy 21), trisomy 13, and trisomy 18 (9). Its involvement in glucose regulation is notable, as reduced PAPP-A levels may contribute to glucose intolerance and the development of gestational diabetes. Assessing PAPP-A levels may offer important insights for predicting and addressing metabolic disorders in pregnancy (8,10).

Research examining the relationship between PAPP-A levels and the risk of diagnosing GDM has produced varying outcomes, emphasizing the absence of a clear consensus in the current scientific literature(10-14).

The aim of this study is to investigate whether PAPP-A levels are associated with the risk of developing GDM. Additionally, the study evaluates the potential value of PAPP-A as a stand alone biomarker in predicting the risk of GDM.

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MATERIAL AND METHOD

From July 2021 to December 2022, a tertiary care maternity hospital hosted this prospective observational study. The study enrolled singleton pregnant women aged 18 to 45 years, with PAPP-A and free β human chorionic gonadotrophin (free β-hCG) levels measured between 11 and 14 weeks of gestation for fetal aneuploidy screening. A 75 g oral glucose tolerance test (OGTT) was also conducted during the study period.

Using a 75 g OGTT, GDM screening was carried out between weeks 24 and 28 of pregnancy. Patients with pregestational diabetes, those using immunosuppressive medication, those having chronic illnesses or infections identified prior to pregnancy, those who had numerous pregnancies, and those on hormone therapy were not included. Fetal abnormalities identified prenatally were also excluded. Additionally excluded were those having obstetric problems such hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, pre-eclampsia, or prenatal hypertension. The research protocol received approval from the Local Ethics Committee (approval number E2-21-513). During patient interviews, the following information was noted: smoking, age, parity, gestational week. Two milliliters of venous blood were drawn and placed in yellow-capped BD Vacutainer® SSTTM (Serum Separator Tube) tubes for aneuploidy screening. The tubes were then left to clot for twenty minutes. Serum was subsequently extracted from the samples by centrifuging them for 15 minutes at 1000 × g in a NÜVE NF 800R Refrigerated Centrifuge. Serum free β-Hcg and PAPP-A levels were assessed using the Siemens Immulite 2000 XPi Immunoassay System (Siemens, Los Angeles, USA) and the Chemiluminescence Immunoassay (CLIA) method. The PRISCA 5 Prenatal Risk Assessment Software was used to analyze the findings. 161 (28.09%) of the 573 pregnant women developed GDM. GDM cases had significantly lower maternal PAPP-A MoM concentrations than the control group (p=0.042). Furthermore, the low PAPP-A group had significantly greater maternal age (p=0.036) and body mass index (BMI) (p<0.01), respectively. The PAPP-A multiple of the median (MoM) level threshold value for predicting GDM was established by ROC analysis. 161 (28.09%) of the 573 pregnant women developed GDM. In the group with low PAPP-A levels, both maternal age (p=0.036) and BMI (p<0.01) were significantly higher. A p-value of less than 0.05 is regarded as suggestive of statistical significance, and statistical analyses were conducted using SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA). Frequency distributions were used to summarize categorical data, while mean±SD or median values were used to express continuous variables along with the interquartile range (IQR). Fisher's exact test or the chi-square test were used for categorical variable analysis, and the independent t-test or the Mann-Whitney U test, as appropriate, were used for group comparisons for continuous variables.

RESULTS

This study comprised 573 pregnant women with singleton pregnancies. 412 (71.91%) of the participants did not have a GDM diagnosis, while 161 (28.09%) did. Two groups of participants were formed based on their PAPP-A levels; PAPP-A levels were normal in 453 women and low in 121 women. Pregnant with GDM exhibited a median PAPP-A MoM of 0.68 (interquartile range [IQR]: 0.30–1.63), whereas pregnant without GDM had a median value of 0.85 (IQR: 0.32–2.49) (Table 1). GDM was linked to a low serum PAPP-A MoM level (p=0.042). However, women with and without GDM did not significantly differ in their levels of free β-hCG (p=0.801) (Table 2).

Table 1. Maternal and pregnancy characteristics of the study population characteristics PAPP-A MoM

	PAPP-A MoM<0.4 (n=120)	PAPP-A MoM≥0.4 (n=453)	p-value
Maternal age	32.61 (±4.8)	29.5±5.4	0.036
Gravida	2.4±1,6	1.9±1	0.000
Weight (kg)	70.4±10	68.1±11	0.023
BMI (kg/m²)	30.2±4.4	27.6±3.4	0.000
Smoker (n)	2 (1.66%)	6 (1.32%)	0.019
Gestational age	12	11.7±0.2	0.468

BMI: body mass index, PAPP-A : pregnancy-associated plasma protein-A, MoM: multiple of the median

Table 2. Median values of maternal serum biomarkers and nuchal translucency length in women with Gestational diabetes mellitus and normal pregnancies

	GDM group (n=161)	Non-GDM group (n=412)	P value
free-βhCG MoM, median (IQR)	0.76 (0.38-3.6)	0.68 (0.45-2.6)	0.801
free-βhCG (MU/L) median (IQR)	25.9 (14.7-146)	30.4 (14.3-97)	0.941
PAPP-A MoM, median (IQR)	0.68 (0.30-1.63)	0.85 (0.32-2.49)	0.042
PAPP-A (MU/L) median (IQR)	2.24 (0.60-10)	3.57 (0.47-10)	0.06

Data are presented as median (IQR); The mann-Whitney test was employed to compare the numerical variables between groups Gestational diabetes mellitus (GDM), free β-human chorionic gonadotropin (fβ-hCG), Interquartile range (IQR), Multiple of the median (MoM), pregnancy associated plasma protein A (PAP-A)

The independent risk factors linked to GDM were found using binary logistic regression analysis. The study discovered that lower PAPP-A MoM levels (OR=0.893, p=0.020), older maternal age (OR=1.030, p=0.001), and greater maternal weight (OR=1.028, p=0.001) were significant independent risk factors for GDM (Table 3). ROC analysis revealed that the PAPP-A MoM concentration threshold value for predicting GDM was 0.99. This threshold showed 52.3% sensitivity and 51.7% specificity. Its area under the curve (AUC) was 0.527, with a 95% CI of 0.46–0.59 (Figure 1).

Table 3. Investigation of the risk factors for GDM using binary logistic regression analysis OR 95%CI SE P value

	OR	95% C.I.for RR		P value
		Lower	Upper	
PAPP-A MoM	0.893	0.807	0.990	0.020
Maternal age	1.030	1.022	1.034	0.001
Weight	1.028	1.026	1.034	0.001

Binary logistic analysis was used to evaluate the relationship between GDM and maternal factors Odds ratio (OR), confidence interval (CI), multiple of the median (MoM), pregnancy-associated plasma protein A (PPAP-A)

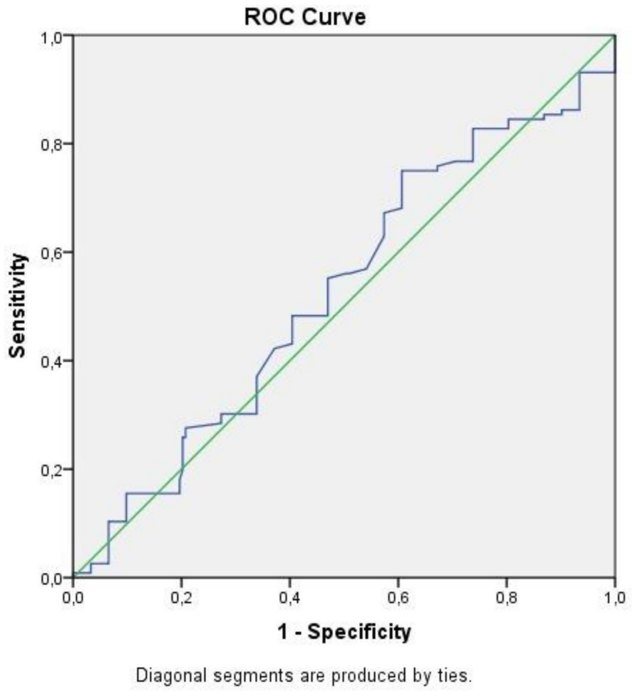

Figure 1. Roc curve statistics for PAP-a MoM level to predict

Analysis of Risk Factors

The following independent risk variables for GDM were found using binary logistic regression analysis:

1. Lower levels of PAPP-A MoM (OR=0.893, 95% CI: 0.807–0.990, p=0.020).
2. Maternal age at advanced age shows a significant association (OR=1.030, 95% CI: 1.022–1.034, p=0.001).
3. Greater maternal weight (p=0.001, OR=1.028, 95% CI: 1.026–1.034). The predictive value of PAPP-A for GDM and the usefulness of PAPP-A levels as a predictive marker for GDM were evaluated using ROC curve analysis. With a PAPP-A MoM threshold of 0.99, 52.3% sensitivity and 51.7% specificity were obtained. The area under the curve (AUC) was 0.473 with a 95% CI of: 0.523–0.561, suggesting that PAPP-A's prognostic power as a stand-alone marker for GDM is limited (Table 3).

DISCUSSION

This research explored the connection between PAPP-A and the likelihood of developing GDM. The results indicated that maternal PAPP-A levels were notably lower in individuals with GDM compared to those without, consistent with prior studies linking decreased PAPP-A levels to adverse pregnancy outcomes, including GDM (10-12,15-17). Despite this correlation, the standalone predictive value of PAPP-A for GDM was found to be modest, emphasizing the need for further exploration of integrated approaches to risk prediction.

Role of Insulin Resistance (IR) in GDM remains the cornerstone of GDM pathophysiology. Pregnancy naturally induces a state of IR, which is exacerbated due to decreased β-cell function and insulin receptor activity in adipose tissue (18,19). In this study, both age and BMI were significantly higher in GDM patients, consistent with earlier reports (1,19). Interventions aimed at improving maternal glucose metabolism in early pregnancy may reduce GDM risk; however, late diagnosis often limits the effectiveness of preventive measures (20).

PAPP-A is plays a key role in modulating the activity of insulin-like growth factors (IGFs) by breaking down IGF binding proteins, thereby affecting the bioavailability of IGFs. It has been extensively studied in various scenarios, including its significance during pregnancy and its association with conditions such as GDM and diabetic nephropathy. This mechanism is critical for placental development, functionality, and fetal growth (8-10). IGFs also play a pivotal role in modulating insulin sensitivity. Reduced PAPP-A levels in early pregnancy may impair IGF function, thereby contributing to glucose intolerance and IR. Supporting this hypothesis, recent meta-analyses and studies have linked low PAPP-A levels with GDM and other complications, including fetal growth restriction and preeclampsia (9,21-23). However, the predictive capacity of PAPP-A remains controversial, as sensitivity and specificity for GDM prediction are limited (24).

In some studies, no association has been found between PAPP-A and GDM (13,14,25). This inconsistency may

be attributed to differences in patient characteristics, diagnostic criteria, and varying severity of GDM. PAPP-A levels did not alter in women with GDM who needed insulin treatment between weeks 11 and 14 of pregnancy, according to Husslein et al. (26).

Therefore, combining PAPP-A measurements with other clinical tests may be necessary for better prediction of GDM risk. Since it was not within the scope of our study, we did not combine or compare other routinely checked markers with PAPP-A for GDM prediction (27).

Ethnic Variations in Biomarker Levels

Ethnic diversity is a critical factor. Variations in PAPP-A, free β-hCG, and placental growth factor (PIGF) levels across ethnic groups have been documented, with Asian women generally exhibiting higher PAPP-A levels and lower PLGF levels than in Caucasian populations (28). Despite these differences, studies investigating PAPP-A and its relationship with GDM in specific populations, such as Chinese women, remain limited (28). Future research should address these gaps to develop population-specific predictive models that account for ethnic variability.

Study Limitations

The primary limitations of this study include its single-center design and the relatively small sample size, which may restrict the generalizability of the findings to broader populations. Second, we did not classify GDM cases by severity or type, which may influence biomarker associations. Third, adverse neonatal and maternal outcomes associated with GDM were beyond the scope of this research. Future studies with larger, multicenter cohorts should explore the combined predictive value of PAPP-A with other clinical and biochemical markers. Additionally, longitudinal studies assessing the dynamic changes in biomarker levels throughout pregnancy could provide deeper insights into the temporal relationships between biomarkers and GDM development.

CONCLUSION

In conclusion, while first-trimester PAPP-A levels were inversely associated with GDM risk, their predictive accuracy as a standalone marker was limited. Integrating PAPP-A with other biomarkers and maternal risk factors holds potential for enhancing early GDM prediction. Given the rising prevalence of GDM and its implications for maternal and neonatal health, further research is essential to establish robust, clinically applicable predictive models for early intervention and improved outcomes.

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