

# The predictive value of the first trimester combined test for gestational diabetes mellitus

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## ABSTRACT:

**Objectives:** To investigate the predictive importance of first trimester combined test markers pregnancy-associated plasma protein-A (PAPP-A), human chorionic gonadotropin  $\beta$  ( $\beta$ -hCG) and nuchal translucency (NT) for gestational diabetes mellitus (GDM).

**Material and methods:** Pregnant women which both first trimester combined test and GDM screening were performed during antenatal follow-up were included in this retrospective case-control study. The cases were divided into two groups as GDM screening positive and negative. Demographic, clinical and laboratory data of both groups were compared. Predictive tests were applied to the first trimester combined test data for the detection of GDM.

**Results:** A total of 378 patients, 171 (45.2%) in the control group and 207 (54.8%) in the GDM group. The age (control:  $30.9 \pm 5.2$ ; GDM:  $30.5 \pm 5.1$ ;  $p = 0.844$ ) and NT (control:  $1.254 \pm 0.289$ ; GDM:  $1.319 \pm 0.299$ ;  $p = 0.074$ ) data of the groups were statistically similar.

MoM PAPP-A (GDM:  $0.967 \pm 0.685$ ; control:  $1.191 \pm 0.624$ ;  $p < 0.001$ ) and MoM f- $\beta$ hCG (GDM:  $0.9 \pm 0.602$ ; control:  $1.103 \pm 0.746$ ;  $p = 0.001$ ) levels of the GDM group were lower than the control group.

In the binary logistic regression model, MoM PAPP-A and MoM f- $\beta$ hCG variables were found to be effective on GDM. In the ROC analysis of these variables, the MoM PAPP-A (0.654) had the highest area under the curve. According to the optimum cut-off point ( $\leq 0.885$ ) of the MoM PAPP-A, we found a sensitivity of 66.7% and a specificity of 65.50% for predicting GDM.

**Conclusions:** Our study showed that serum PAPP-A and f- $\beta$ hCG MoM values, which are among the first trimester combined test parameters, can be used in the early pregnancy period for the prediction of GDM.

**Key words:** gestational diabetes; pregnancy-associated plasma protein-A; chorionic gonadotropin; nuchal translucency

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## INTRODUCTION

Hyperglycemia that is diagnosed for the first time during pregnancy and is confirmed by appropriate laboratory tests is called gestational diabetes mellitus (GDM) [1]. One in six live births is affected by hyperglycemia during pregnancy, and the incidence of GDM increases with increasing obesity prevalence and advancing maternal age [2]. Therefore, GDM screening via glucose loading test is recommended between 24–28 weeks of gestation for every pregnant woman without any risk factors in our country, as in many countries. The first trimester combined test, whose components are pregnancy-associated plasma protein-A (PAPP-A), human chorionic gonadotropin  $\beta$  ( $\beta$ -hCG), and fetal nuchal translucency (NT) detected by ultrasonography, is also recommended for every

pregnant woman between 11–14 weeks of gestation to determine the risk of trisomies 15, 18 and 21. Since PAPP-A, one of the first trimester combined test components, is a positive regulator of insulin-like growth factors (IGF) [3], many studies have investigated its relationship with GDM [4–6].

The severity and duration of maternal hyperglycemia are associated with complications such as spontaneous abortion, fetal macrosomia, anomalies and death; neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, and maternal preeclampsia/eclampsia [7]. Hence, examining the components of the combined test applied in the first trimester will enable the early detection of GDM candidates without any previous risk factors and thereby prevent these complications [8].

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In this study, we aimed to investigate the predictive value of the first trimester combined test parameters, which are recommended for every pregnant woman between 11–14 weeks of gestation in antenatal follow-up, in detecting cases with GDM risk in the period until the glucose loading test recommended for each pregnant woman between 24–28 gestational weeks.

## MATERIAL AND METHODS

For this retrospective cohort study, pregnant women monitored in Izmir Katip Celebi University Atatürk Training and Research Hospital Gynecology and Obstetrics Clinic between January 1, 2017 and December 1, 2021 were screened. The study was carried out in accordance with the ethical standards stipulated in the 1964 Declaration of Helsinki and its 2013 revision. Informed consent was not obtained from the patients due to the retrospective design of the study and the anonymous data used in the analysis. An ethics committee approval was obtained from our institution prior to our study (#0571/2021).

Women with a single pregnancy and newly diagnosed GDM, and a control group of healthy pregnant women without any endocrinological disease, were included in the study. Pregnant women with a previous diagnosis of GDM, ongoing history of diabetes mellitus, or an additional systemic disease were excluded from the study groups. In addition, cases in the GDM risk group whose fasting blood glucose was detected at the first control were also excluded from the study.

In our clinic, the one-step 75-g oral glucose tolerance test (OGTT) recommended by the International Association of Diabetes and Pregnancy Working Groups [9] is applied for the screening and diagnosis of GDM (Tab. 1).

The first trimester combined test, whose components are PAPP-A, f-βhCG and nuchal translucency (NT), is performed at 11–14 weeks of gestation in our clinic.

Demographic, clinical, laboratory, and ultrasonographic findings of the cases were obtained retrospectively through the hospital data operating system.

The cases were divided into two groups according to GDM screening as negative and positive screening. The groups were analyzed comparatively with the data obtained in the study. In addition, ROC analyzes were performed to determine sensitivity, specificity, and positive and negative predictive values.

Descriptive statistics were expressed as number (n), percentage (%), and mean ± standard deviation values ( $\bar{x} \pm ss$ ). The normal distribution of the numerical data was evaluated with the Shapiro Wilk normality test and by the Q-Q plots. Homogeneity of variances was evaluated with a Levene's test. Data of non-normally distributed variables PAPP-A, Mom PAPP-A, f-βhCG, and MoM

**Table 1. One-step screening test for gestational diabetes**

75 g oral glucose tolerance test parameters*		
Fasting plasma glucose	Hour 1	Hour 2
≥ 92	≥ 180	≥ 153

\*Any of these three parameters above the limit value is sufficient for diagnosis

f-βhCG were transformed in base 10 logarithms. Groups were compared using an independent two-sample *t* test for normally distributed variables and a Mann-Whitney *U* test for non-normally distributed variables. Variables with  $p < 0.10$  significance value in univariate analyses were included in the binary logistic regression analysis to determine the factors affecting GDM. Backward Wald method was used in binary logistic regression analysis. Binary logistic regression analysis results were given as  $\beta$  regression coefficients, standard error of the regression coefficients (se), odds ratios [Exp ( $\beta$ )], 95% confidence intervals of odds ratios, Wald statistics and significance values. The performances of the variables thought to predict GDM were evaluated by ROC curve analysis.

A *p* value of  $<0.05$  was considered statistically significant.

IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) statistical software was used for all calculations.

## RESULTS

A total of 378 patients with 171 (45.2%) in the control group and 207 (54.8%) in the GDM group were included in the study. Of the 207 GDM patients, blood sugar was regulated by diet in 157 (75.8%) and insulin use in 50 (24.2%).

Comparative analysis results of the control and GDM groups are shown in Table 2.

To determine the factors affecting GDM, regression analysis was applied to the MoM f-βhCG and MoM PAPP-A variables with  $p < 0.05$  value in Table 2. The binary logistic regression model (Backward Wald) found MoM PAPP-A and MoM f-βhCG to be effective on GDM (Tab. 3).

According to Table 3, the risk of GDM decreases by 1.89 (1/0.529) fold with the increase in MoM PAPP-A and 1.81 (1/0.553) fold with the increase in MoM f-βhCG. According to Wald statistics, the variable with the highest effect on GDM was PAPP-A.

The predictive performances of MoM PAPP-A and MoM f-βhCG variants were evaluated by receiver operating characteristic (ROC) analysis (Fig. 1). In the ROC analysis, the MoM PAPP-A variable yielded the highest area under the curve, with an optimum cut-off point of 0.885. According to this value, sensitivity and specificity were calculated as 66.67% and 65.50%, respectively (Tab. 4).

**Table 2.** Comparison of the parameters between groups

Data	Groups		Test statistics	
	Control n = 171	GDM n = 207	Test value	p-value
Age [year] x ± SD	30.9 ± 5.2	30.5 ± 5.1	t = 0.202	0.844
MoM PAPP-A <sup>†</sup> x ± SD	1.191 ± 0.624	0.967 ± 0.685	t = 3.329	p < 0.001
MoM f-βhCG <sup>†</sup> x ± SD	1.103 ± 0.746	0.9 ± 0.602	t = 2.920	0.001
NT x ± SD	1.254 ± 0.289	1.319 ± 0.299	t = 2.127	0.070

<sup>†</sup>Comparisons were made on logarithm base 10 transformed data; GDM — gestational diabetes mellitus; t — two independent samples t-test statistic; x — mean; SD — standard deviation; PAPP-A — pregnancy-associated plasma protein-A; MoM — multiple of median; βhCG — human chorionic gonadotropin β; NT — nuchal translucency

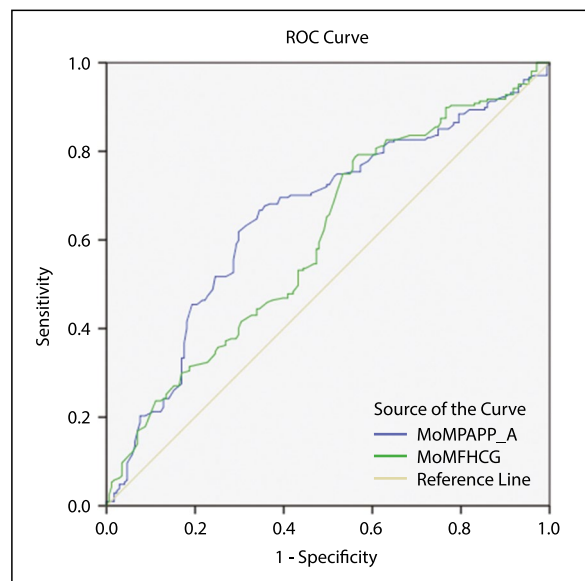
**Table 3.** Binary logistic regression analysis of factors affecting gestational diabetes mellitus

Data	β	se	Wald	p	Exp (β)	95% CI for Exp (β)
MoM PAPP-A	-0.638	0.282	5.094	0.024	0.529	0.304–0.920
MoM f-βhCG	-0.592	0.301	3.863	0.049	0.553	0.307–0.998

β — regression coefficient, se — standard error; CI — confidence interval; PAPP-A — pregnancy-associated plasma protein-A; MoM — multiple of median; βhCG — human chorionic gonadotropin β

## DISCUSSION

The key finding in our study was the statistically significantly lower MoM PAPP-A (control: 1.191 ± 0.624; GDM: 0.967 ± 0.685; p < 0.001) and MoM f-βhCG (control: 1.103 ± 0.746; GDM: 0.9 ± 0.602; p = 0.001) levels in the GDM group compared to the control group. In the binary logistic regression model, MoM PAPP-A and MoM f-βhCG variables were found to be effective on GDM. In the ROC analysis of these variables, MoM PAPP-A (0.654) had the highest area under the curve, and at the optimum cut-off point (≤ 0.885), the sensitivity of GDM prediction was 66.7%, and specificity was 65.50%. In the literature on the relationship between first-trimester combined test parameters and GDM, studies that found only MoM PAPP-A levels to be significantly lower in GDM cases [8, 10–13] (10 are much more common than studies reporting significantly lower levels for both MoM PAPP-A and MoM f-βhCG [4, 14, 15]). This may be related to the fact that PAPP-A is the protease of insulin-like growth factor binding protein 4 (IGFBP-4) [16]. The reduction in PAPP-A results in higher levels of IGF-binding protein, lower levels of free IGF, and hence hyperglycemia. For this reason, researchers focused on PAPP-A level in the pathogenesis of GDM, and conducted many studies only investigating the relationship between PAPP-A level and GDM and found this relationship statistically significant [17–20]. However, there are also studies that could not find a significant relationship between first-trimester combined test parameters and GDM



**Figure 1.** Receiver operating characteristic (ROC) analyses of MoM PAPP-A and MoM f-βhCG parameters; PAPP-A — pregnancy-associated plasma protein-A; MoM — multiple of median; FHCG — free human chorionic gonadotropin

[21–24]. This contradictory finding may be explained by the multifactorial pathogenesis of GDM. Therefore, more research involving other possible risk factors is needed to reveal the association of low PAPP-A and f-βhCG levels with GDM.

**Table 4. Performances of variables in predicting gestational diabetes mellitus**

Data	AUC	p	Cut-off	Sensitivity	Specificity	PPV	NPV
MoM PAPP-A	0.654	< 0.0001	≤ 0.885	66.67	65.50	70.1	61.9
MoM f-βhCG	0.603	0.001	≤ 0.990	74.40	46.80	62.9	60.2

AUC — area under the curve; PPV — positive predictive value; NPV — negative predictive value; PAPP-A — pregnancy-associated plasma protein-A; MoM — multiple of median; βhCG — human chorionic gonadotropin β

In our study, the area under the curve in the ROC analysis to determine the predictive performance of MoM PAPP-A and MoM f-βhCG markers for GDM was 0.654 and 0.603, respectively. In a case-control study involving 596 GDM cases, Visconti et al. found the area under the curve for MoM PAPP-A and MoM f-βhCG markers to be 0.479 and 0.488, respectively, that is, statistically insignificant [4]. In the case-control study of Lovati et al. [25] involving 673 GDM cases, the area under the curve for MoM PAPP-A was found to be 0.70. These different findings in the literature suggest that besides low PAPP-A and f-βhCG levels, other factors may also play a role in the pathogenesis of GDM.

Consistent with similar studies in the literature investigating the relationship between first-trimester combined test parameters and GDM [4, 15, 26], our study found no significant difference in NT between GDM and control group cases.

There was no statistically significant difference between the ages of the subjects included in the GDM and control groups. In the literature, there are case-control studies that found the age difference to be insignificant [6, 17], as well as studies that found the age to be significantly higher in the GDM group [4, 10, 15].

The strength of our study was that the number of cases was similar (12) or higher [6, 11, 17] with other retrospective case-control studies in the literature. Due to the retrospective nature of the study, in the posthoc type power analysis ( $\alpha = 0.05$ ) it was calculated that the present study sample size corresponded to a power of 91.4%. The weakness of our study is the limited randomization between groups due to its retrospective nature. The most important limitation of our study is that height data could not be obtained from patient files in most of the cases included in the study. Thus we could not calculate body mass index and could not use these data to compare between groups. We believe that these limitations can be overcome with future randomized prospective case-control studies.

## CONCLUSIONS

The development of predictive parameters for MoM PAPP-A and MoM f-βhCG will contribute to the diagnosis of GDM in the early weeks of pregnancy and the management of possible maternal and fetal complications.

## Conflict of interest

All authors declare no conflict of interest.

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