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The predictive value of first trimester maternal serum pregnancy-associated plasma protein-A (PAPP-A) level in predicting gestational diabetes mellitus

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ABSTRACT

Aims: The aim of this study is to evaluate the predictive value of first trimester biochemical markers in the subsequent development of gestational diabetes mellitus.

Methods: Data were retrospectively collected from the file records of 361 pregnant patients, who were admitted to the 1st Obstetrics and Gynecology Clinic at Şişli Etfal Education and Training Hospital for first trimester prenatal screening test between 11-14 weeks of their gestation and who later had undergone 50 gram glucose challenge test at 24-28 weeks of their gestation, between November 2007 and February 2011. Age, patient weight, Crown rump length (CRL), gestational week, Pregnancy-Associated Plasma Protein-A (PAPP-A) concentration, PAPP-A multiple of median (MoM) value, Beta-human koryonik gonadotropin (B-HCG) concentration, B-HCG MoM value, 50 and 100 g oral glucose challange test result were recorded from the files. Gestational diabetes was diagnosed according to National Diabates Data Grup cutt-off values and criteria. The association between first trimester biochemical markers and subsequent development of gestational diabetes was evaluated.

Results: In this study low PAPP-A and/or HCG MoM values and increased Nuchal translucency (NT) MoM values were found to be statistically significant for subsequent development of gestational diabetes.

Conclusion: GDM is an important health problem that carries many risks of complications for both mother and fetus. Pregnant women with GDM may have high blood sugar levels before diagnosis at 24 weeks of gestation, so fetal growth may be negatively affected by maternal hyperglycemia. Use of first trimester screening maternal serum biomarkers may lead to early diagnosis of GDM and interventions to improve maternal and fetal outcomes.

Keywords: Fetal screening tests, pregnancy complications, chromosomal anomalies

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease in which the organism cannot benefit sufficiently from carbohydrates, fats and proteins due to insulin deficiency or defects in insulin action, requiring constant medical care. Hyperglycemia resulting from uncontrolled diabetes mellitus can lead to death with acute complications, and impairs the quality of life with long-term chronic complications .

Gestational diabetes mellitus (GDM) is called abnormal carbohydrate intolerance that begins during pregnancy or is detected for the first time during pregnancy.[1] Approximately 7% of all pregnancies are complicated by GDM, and more than 200,000 cases are estimated to occur annually worldwide.[2,3] Studies conducted in different regions in Türkiye have found that the prevalence of GDM varies between 3-8%.[4]

Pregnancies complicated by diabetes mellitus are risky pregnancies that require careful monitoring from both maternal and fetal perspectives. It is a metabolic disorder that can cause morbidity and mortality in various spectrums, from congenital malformations and in utero death in the baby, to hypoglycemia, diabetic ketoacidosis, to an increase in retinopathy, neuropathy and nephropathy in the mother, when adequate glycemic control is not achieved.[5]

Thanks to developing screening programs, diagnosis and treatment protocols, maternal-fetal mortality and morbidity in pregnancies with gestational diabetes have decreased significantly. Despite this, some complications are more common in pregnancies with gestational diabetes, and GDM is still an important risk factor for maternal and neonatal morbidity. In this sense, early diagnosis and treatment is important.

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The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO Study) study published in 2008 showed that an increase in plasma glucose level at any time during pregnancy is associated with an increase in adverse obstetric outcomes such as macrosomia, cesarean delivery, hypoglycemia, preterm birth, dystocia, etc. Riskin-Mashiah et al.[6] reported that there is a relationship between high plasma glucose level in the first trimester and the development of GDM and poor obstetric outcomes. In the light of this information, it can be assumed that if markers that can predict the development of GDM in the early weeks of pregnancy, poor obstetric outcomes that may occur due to gestational diabetes can be prevented with early diagnosis and treatment.

For the first time, the working group of the Royal College of Obstetricians and Gynaecologists (RCOG) talked about first trimester serum markers in 1997, which could be as effective as specific serum markers used in Down syndrome screening at 15-22 weeks of gestation. The best known serum markers used in the first trimester are pregnancy-associated plasma protein-A (PAPP-A) and free beta human chorionic gonadotropin. (Sb-HCG). The detection rate of PAPP-A and sb-HCG for Down syndrome at 9-11 weeks of gestation is 60% with 5% false positivity.[7]

It is known that abnormal maternal serum biochemical markers examined in the first trimester are associated with poor obstetric outcomes in the absence of fetal aneuploidy and neural tube defects.[8,9] It has been shown in many studies that especially low pregnancy-associated plasma protein-A (PAPP-A) is associated with poor obstetric outcomes such as spontaneous fetal losses, low birth weight, intrauterine growth restriction (IUGR), and preeclampsia.[10-13]

Whether gestational diabetes, as an important pregnancy complication, has a relationship with abnormal maternal serum biochemical markers in the first trimester has not been adequately examined by studies, and a few studies in the literature have found a significant relationship, especially between low PAPP-A and gestational diabetes.[14,15]

The aim of this study is to investigate the relationship between first trimester abnormal maternal serum biochemical marker levels and the risk of developing gestational diabetes in chromosomally normal pregnant women.

METHODS

This study is produced from a master thesis in 2011. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data were retrospectively collected from the file records of 361 pregnant patients, who were admitted to the 1st Obstetrics and Gynecology Clinic at Şişli Etfal Education and Training Hospital for first trimester prenatal screening test between 11-14 weeks of their gestation and who later had undergone 50 gram glucose challenge test at 24-28 weeks of their gestation, between November 2007 and February 2011.

CRL measurement, weeks of gestation based on CRL measurement, PAPP-A concentration, PAPP-A MOM value, β-HCG concentration, β-HCG MOM value, smoking, presence of pregestational diabetes and presence of twin pregnancy were recorded by examining pregnant patient files.

NT was measured in accordance with the Fetal Medicine Foundation criteria using the Siemens model Acusun Antares P.E. (U.S.A) transabdominal CH6-2 probe.

Serum PAPP-A, β -HCG concentrations were obtained by Şişli Etfal Training and Research Hospital Biochemistry Clinic using the Enhanced Chemiluminescent method on the Immulite 2000 autoanalyzer (Siemens Brand Immulite 2000 model Fully automatic immunoassay autoanalyser). Using the Prisca 3.4 screening program, PAPP-A and β-HCG MOM values were calculated by taking the information in the form filled out for the first trimester screening test.

Pregnant women whose 1st hour plasma glucose level was 140 mg/dl and above in the 50-gram oral glucose screening test at 24-28 weeks of gestation were subjected to a 100-gram oral glucose screening test. In 100 g OGTT, after blood was taken for fasting blood sugar, blood sugar levels were measured again at 1, 2 and 3 hours.The threshold value for fasting blood sugar is 105 mg/dl, the threshold value for 1st hour postprandial blood sugar is 190 mg/dl, the threshold value for 2nd hour postprandial blood sugar is 165 mg/dl, the threshold value for 3rd hour postprandial blood sugar is 145 mg/dl received. If two or more of the blood sugar levels measured exceed the threshold values, gestational diabetes mellitus was diagnosed. Plasma glucose levels recommended by the National Diabetes Data group were accepted as the threshold value for the diagnosis of gestational diabetes mellitus.

Pregnancies with multiple pregnancies, pregestational diabetes, fetal chromosomal disease diagnosis, and structural anomalies seen in ultrasonographic examination were not included in the study.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used for statistical analysis.

While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median), Student's t test is used for intergroup comparisons of normally distributed parameters; Mann Whitney U test was used for intergroup comparisons of parameters that did not show normal distribution. Chi-Square test was used to compare qualitative data. Significance was evaluated at $p<0.05$ level.

RESULTS

The ages of the cases ranged between 18 and 42 years, and the average was 28.45±5.67 years. When looking at weight measurements, it varies between 40 and 112 kg and the average is 65.19±12.54 kg. Pregnancy weeks vary between 11 and 14 weeks, and the average is 12.66±0.67 weeks.

PAPP-A mlU/ml measurements range between 0.26 and 13.70, and the average is 2.05±1.61 mlU/ml. PAPP-A mom measurements also vary between 0.14 and 4.28, and the average is 0.89±0.54 mom.B-HCG ng/ml measurements of the cases ranged between 10 and 200, and the average was 45.82±31.11 ng/ml. B-HCG mom measurements vary between 0.28 and 4.96, and the average is 1.20±0.76 mom. NT mom measurement also varies between 0.47 and 1.91, and the average is 0.96±0.21 mom. The 50 gram oral glucose tolerance test result was high in 42.9% (n=155) of the participants and GDM is seen in 25.5% (n=92) of the participants. Distribution of general features was presented in **Table 1**.

Table 1. Distribution of general features		
(n=361)	Min-Max	Mean±SD
Age (year)	18-42	28.45±5.67
Weight (kg)	40-112	65.19±12.54
Week Of Pregnancy	11.14-14.00	12.66±0.67
CRL (mm)	35.6-82.0	63.05±8.99
PAPP-A (mlU /ml)	0.26-13.70	2.05±1.61
PAPP-A (mom)	0.14-4.28	0.89±0.54
B-HCG (ng/ml)	10-200	45.82±31.11
B-HCG (mom)	0.28-4.96	1.20±0.76
FBG	62-146	85.70±9.85
50 gr OGTT	66-226	137±34.70
Nt (mom)	0.47-1.91	0.96±0.21

There is a statistically significant difference between the average ages according to gestational diabetes status (p<0.01). The ages of cases with gestational DM are significantly higher than those without. Also there is a statistically significant difference between weight averages according to gestational diabetes status (p<0.01). The weight of cases with gestational DM is significantly higher than those without. No statistically significant difference between the smoking rates of cases with and without gestational diabetes (p>0.05). Descriptive Characteristics According to Gestational Diabetes was presented in Table 2.

Table 2. Evaluations of descriptive characteristics according to gestational diabetes mellitus (GDM)			
Table	GDM		p
	Yes (n=92) Maen+SD	NO (n=269) Mean+SD	
Age (year)	32.01±5.06	27.23±5.35	0.001**
Weight (kg)	69.39±11.90	63.75±12.45	0.001**
+Smoking	n (%)	n (%)	
Yes No	12 (13.0%) 80 (87.0%)	41 (15.2%) 228 (84.8%)	0.607
Student t test +Ki kare test			

There is a statistically significant difference between β-HCG ng/ml measurements according to gestational diabetes status (p<0.05). The average β-HCG ng/ml measurement of those with gestational diabetes is significantly lower than those without, and the median is 32.90. Also there is a statistically significant difference between β-HCG mom measurement according to gestational diabetes status (p<0.05). The mean β-HCG mom measurements of those with gestational diabetes are significantly lower than those without, and the median is 0.92. Evaluation of β-HCG measurements according to gestational diabetes status was presented in Table 3.

Table 3. Evaluation of Beta-human korionik gonadotropin (β-HCG) measurements according to gestational diabetes status				
GDM	β -HCG (ng/ml)		β -HCG (mom)	
	Ort±SD	Median	Ort±SD	Median
Yes	39.79±27.94	32.90	1.07±0.69	0.92
No	47.88±31.91	40.80	1.25±0.77	1.06
P	0.017*		0.032*	
Mann-Whitney U test, *p<0,05				

There is a statistically significant difference between PAPP-A mlU/ml measurements according to gestational diabetes (p<0.05). The mean PAPP-A of those with gestational diabetes is significantly lower than those without gestational diabetes, with a median of 1.40. Also there is a statistically significant difference between PAPP-A mom measurements according to gestational diabetes (p<0.01). The mean PAPP-A mom of cases with gestational diabetes is significantly lower than those without gestational diabetes and the median is 0.68. PAPP-A Evaluations According to Gestational Diabetes was presented in Table 4.

Table 4. Pregnancy-associated plasma protein-A PAPP-A evaluations according to gestational diabetes				
GDM	PAPP-A mlU/ml		PAPP-A mom	
	Mean±SD	Median	Mean±SD	Median
Yes	1.71±1.10	1.40	0.76±0.39	0.68
No	2.17±1.74	1.68	0.93±0.58	0.78
p	0.017*		0.009**	
Mann-Whitney U test, *p<0,05, **p<0,01				

Based on this significance, calculation of the cut-off point for PAPP-A mom was considered. ROC analysis was used to determine the cut-off point for PAPP-A MoM.In cases with a PAPP-A MoM level of 0.70 and below, the sensitivity in detecting gestational diabetes was found to be 53.26%, the specificity was 57.99%, the positive predictive value was 30.25% and the negative predictive value was 78.39%. ROC analysis was given in Figure.

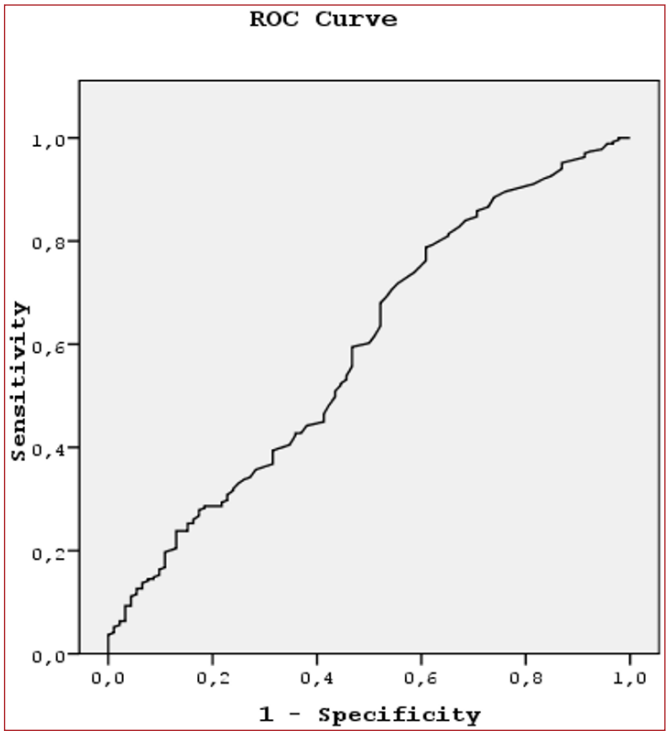

Figure. ROC curve obtained for PAPP-A MoM
The area under the ROC curve obtained was found to be 59.2%, with a standard error of 3%.

DISCUSSION

Gestational diabetes is defined as glucose intolerance that begins and is first detected during pregnancy.[16] It is an important health problem that can cause both maternal and fetal mortality and morbidity if glycemic control is not provided with adequate treatment at the time of diagnosis. Nowadays, screening tests performed in the second trimester of pregnancy are used to diagnose gestational diabetes, but after diagnosis, the time period remaining for clinicians to find the ideal treatment will be narrowed. There are various metabolic changes in the blood of pregnant women who will develop gestational diabetes in the early stages of pregnancy before the diagnosis of gestational diabetes and if these changes are detected, early diagnosis and treatment may be possible.

In the present study, in the light of this information, we investigated whether PAPP-A level, which is known to have an effect on fetal growth and development, is a serum marker that can be used to diagnose gestational diabetes in the early period.

Although the relationship between PAPP-A level and pregnancy complications such as preeclampsia, low birth weight, and preterm birth has been examined by many researchers, its relationship with gestational diabetes has been mentioned in only a few studies.

Spencer et al.[7] investigated the relationship between first trimester maternal serum PAPP-A and sb-HCG and second trimester uterine artery Doppler findings and pregnancy complications. A significant relationship was found between low PAPP-A and preeeclampsia, fetal growth restriction and preterm birth (in case of PAPP-A <0.844, <0.813 and <0.928 MOM, respectively). No relationship was found between Sb-HCG levels and pregnancy complications.

Krantz et al.[17] found that low or high levels of sb-HCG, PAPP-A and NT values carry an increased risk of intrauterine growth retardation, premature birth, preeclampsia and stillbirth.

In a prospective study conducted by Smith et al.[9] on 8839 pregnant women between 8-14 weeks of gestation, it was determined that low PAPP-A levels carried an increased risk of intrauterine growth retardation, premature birth, preeclampsia and stillbirth.

In a retrospective study conducted by Beneventi et al.[13] in 2011 on 456 singleton pregnant women, the relationship between PAPP-A levels measured in the first trimester and the development of gestational diabetes was investigated. The average PAPP-A MOM value in pregnant women who developed gestational diabetes was 0.7, and the average PAPP-A MOM value in the control group was 1.2, which was significantly lower than the control group (P<0.001).

In the retrospective case control study conducted by Xiao et al.[19] on 599 pregnant women with GDM and 986 euglycemic pregnant women, the average PAPP-A MOM value was found to be 0.88 in pregnant women with GDM and 0.97 in euglycemic pregnant women, and it was found to be statistically significant (p<0.001).

In the retrospective case-control study conducted by Cui et al.[20] on 4872 patients, the PAPP-A MOM value was found to be lower in pregnant women with GDM, 0.86, and 0.97 in patients without GDM.

In the study conducted by Ren et al.[21] on 99 patients, PAPP-A value was found to be lower in pregnant women with GDM than in the control group. The average value was 13.84 ng/L in patients with GDM and 16.96 ng/L in the group without GDM (p<005).

In the prospective study conducted by Ramezani et al.[22] on 284 pregnant women, the relative risk of GDM in patients with decreased PAPP-A levels was estimated to be 4.77 times compared to healthy people.

In the retrospective case-control study conducted by Yanachkova et al.[23] on 662 pregnant women, the median PAPP-A adjusted MOM was significantly lower in GDM group compared to the control group (1.2 vs 1.3; p<0.001).

In a retrospective study conducted by Visconti et al.[24] on 2410 pregnant women, they found that there was an increased risk for GDM if the PAPP-A mom value was<1.

In present study, as supports the information in the studuies above, the average PAPP-A MOM level was lower and found to be 0.76 in pregnant women who developed gestational diabetes, and the PAPP-A MOM level was 0.93 in the control group, and the difference is statistically significant (P=0.009).

In a large-scale study conducted by Dugoff et al.[10] on 33,395 pregnant women, the relationship between PAPP-A MOM value and pregnancy complications was investigated. A relationship has been found between IUGR, preeclampsia, gestational hypertension and in utero death. Additionally, in this study, a relationship was found between the development of gestational diabetes when the PAPP-A MOM value was taken <10 percentile (PAPP-A MOM<0.52) (P=0.05).

Ong et al.[14] found a significant relationship between low PAPP-A MOM value (<10 percentile) and spontaneous pregnancy losses, IUGR, preeclampsia, and gestational hypertension. In this study, it was found to be statistically significant when the PAPP-A MOM value was below the 10th percentile in pregnant women with gestational diabetes (P=0.002).

In the studies conducted by Dugoff et al.[10] and Ong et al.[14] PAPP-A MOM values were divided into percentiles, and in both studies, the development of gestational diabetes was found to be significantly higher in cases below the 10th percentile. In our study, the PAPP-A MOM value was not considered as a percentile, and when the cut-off value of the PAPP-A MOM value was taken as 0.7, the sensitivity in detecting gestational diabetes was 53.26%; The specificity was determined as 57.99%.

In the study conducted by Kavak et al.[15] on 490 singleton pregnant women in our country, the relationship between PAPP-A value and low birth weight, hypertensive disease, and gestational diabetes was investigated. In their study, no significant relationship was found between PAPP-A level and gestational diabetes. 18 pregnant women with gestational diabetes were included in the study, and we think that this number is insufficient for sampling.

Another result we found in our research is the existence of a relationship between low β-HCG MOM levels and the development of gestational diabetes. In our study, the β-HCG MOM value was found to be 0.92 in the group that developed gestational diabetes and 1.06 in the control group (P=0.032). In the studies conducted by Beneventi et al.[13] Dugoff et al.[10] and Kavak et al.[15] no relationship was found between low β-HCG MOM level and the development of gestational diabetes. In the study conducted by Ong et al.[14] β-HCG levels were found to be significantly low, supporting our study.

In our study, the average age of pregnant women who developed gestational diabetes was significantly higher than the control group (P=0.001). In addition, the average weight of pregnant women who developed gestational diabetes was found to be significantly higher than the control group (P=0.001). In research conducted in the literature; Ben-Haroush et al.[18] Beneventi et al.[13] Body mass index (BMI) was used instead of weight, and BMI was found to be significantly higher in pregnant women who developed gestational diabetes. In our own research, since the heights of the pregnant women were not included in the forms filled out for the first trimester screening tests, we could only compare their weights.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO Study) study published in 2008 showed that an increase in plasma glucose level at any time during pregnancy is associated with an increase in adverse obstetric outcomes such as

macrosomia, cesarean delivery, hypoglycemia, preterm birth, dystocia, etc. Both in our study and in studies reported in the literature, a significant relationship was found between low PAPP-A levels and gestational diabetes. In pregnant women who are found to have low PAPP-A and/or B-HCG MOM levels in the first trimester screening test, we recommend that a direct 75-g OGTT test can be performed to protect the fetus from possible hyperglycemia-related complications in the early period, without undergoing the OGTT screening test between 24-28 weeks. However, this conclusion needs to be supported by large prospective studies.

CONCLUSION

Maternal and fetal complications may occur in the later weeks of pregnancy in pregnant women whose abnormal value is detected in the first trimester screening test but is found to be chromosomally normal. For this reason, these pregnant women should be carefully monitored during their antenatal follow-up and early diagnosis methods should be used. While counseling families for the first trimester screening test, it is important to note that a positive screening test does not always mean a chromosomally diseased baby, but that a positive result may accompany some pathological conditions related to pregnancy (gestational diabetes, preeclampsia, fetal growth restriction, low birth weight, premature birth, fetal death).

ETHICAL DECLARATIONS

Ethics Committee Approval

Since the study is produced from a master thesis in 2011, ethics committee approval is not required.

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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