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The Predictive Value of First and Second Trimester Screening Test Biomarkers in Preeclampsia

Preeklampsi Hastalarında Birinci ve İkinci Trimester Tarama Testi Biyobelirteçlerinin Prediktif Değeri

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ABSTRACT

Objective: This study aimed to determine the predictive value of first and second trimester screening test biomarkers in preeclampsia.

Methods: This was a retrospective case-control study. While 85 patients diagnosed with pre-eclampsia between January 2013-December 2016 constituted the study group, randomly assigned 93 patients with no additional obstetric problems constituted the control group. Demographic characteristics, laboratory results, obstetric outcomes, first and second trimester screening test results were collected from the hospital records.

Results: Of the 85 preeclamptic patients, 32 had mild, 53 had severe pre-eclampsia. When the preeclampsia group was compared with the control group, the low level of pregnancy associated plasma protein-A (PAPP-A) multiples of median (MoM), the high level of human chorionic gonadotropin (hCG) MoM and nuchal translucency (NT) MoM was found to be statistically significant. However, these markers have not been found to be clinically useful for the mild preeclampsia group compared with the severe preeclampsia group. A ROC curve was drawn to show the predictive role of NT MoM, hCG MoM and PAPP-A MoM for preeclampsia. The area under the curve (AUC) was 0.628±0.042 [p=0.003; 95% confidence interval (CI): 0.545-0.711] for NT MoM and 0.697±0.047 (p<0.001; 95% CI: 0.605-0.789) for hCG MoM. The AUC was 0.589±0.044 (p=0.040; 95% CI: 0.503-0.676) for PAPP-A MoM. These results indicate that there were significant relationships between these variables and pre-eclampsia.

Conclusion: Low levels of PAPP-A MoM, high levels of hCG MoM and NT MoM are useful significant predictive markers for prediction of preeclampsia.

Keywords: Pre-eclampsia, prenatal screening, maternal serum tests

ÖZ

Amaç: Bu çalışmanın amacı, preeklampside birinci ve ikinci trimester tarama testi biyobelirteçlerinin prediktif değerini belirlemektir.

Yöntem: Retrospektif bir olgu kontrol çalışmasıdır. Ocak 2013-Aralık 2016 tarihleri arasında preeklampsi tanısı konulan 85 hasta çalışma grubunu oluştururken, rastgele alınan ek obstetrik sorunu olmayan 93 hasta ise kontrol grubunu oluşturmuştur. Demografik özellikler, laboratuvar sonuçları, obstetrik sonuçlar, birinci ve ikinci trimester tarama testi sonuçları hastane kayıtlarından edinilmiştir.

Bulgular: Seksen beş preeklamptik hastanın 32'sinde hafif, 53'ünde şiddetli preeklampsi mevcuttu. Preeklampsi grubu kontrol grubu ile karşılaştırıldığında, gebelik ilişkili plazma protein-A (PAPP-A) MoM seviyesinin düşük, insan koryonik gonadotropin (hCG) MoM ve nukal translüsensi (NT) MoM'un yüksek olduğu bulundu. Ancak, bu belirteçler, şiddetli preeklampsi grubu ile hafif preeklampsi grubu karşılaştırıldığında klinik yararı bulunmamıştır. NT MoM ve hCG MoM ve PAPP-A MoM'un preeklampsi için öngörücü rolünü göstermek için ROC eğrisi çizildi. Eğri altında kalan alan NT MoM için 0,628±0,042 [p=0,003; %95 güven aralığı (GA): 0,545-0,711] ve hCG MoM için 0,697±0,047 (p<0,001; %95 GA: 0,605-

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0,789) idi. PAPP-A MoM için eğri altında kalan alan ise 0,589±0,044 idi (p=0,040; %95 GA: 0,503-0,676) idi. Preeklampsi ile bu değişkenler arasında ilişki olduğunu göstermektedir.

Sonuç: Düşük PAPP-A MoM seviyeleri, yüksek hCG MoM ve NT MoM seviyeleri, preeklampsinin öngörülmesi için faydalı, anlamlı öngörücü belirteçlerdir.

Anahtar Kelimeler: Preeklampsi, prenatal tarama, maternal serum testleri

INTRODUCTION

Preeclampsia is characterized by new-onset hypertension that occurs after 20 weeks of pregnancy.[1] It is a pregnancy specific disease complicating approximately 2-8% of pregnancies.[2] It has been suggested that many pathophysiological mechanisms alone or in combination are responsible for preeclampsia.[3-5] Such heterogeneity of the potential processes leading to preeclampsia has led to the lack of diagnostic methods to identify and prevent women predisposed to developing preeclampsia.

Although no intervention is definitely effective in eliminating the risk of preeclampsia, meta-analyses showed that the use of 60-100 mg aspirin before 16th week of pregnancy in high-risk patients; revealed that preeclampsia can be prevented by 50%.[6,7] and this result brought up the importance of early identification of high-risk pregnant women to take necessary measures to improve perinatal and maternal outcomes.

A recent meta-analysis stated that some angiogenic markers and prediction models were associated with preeclampsia.[8] Biochemical markers or a combination of biochemical and biophysical markers in the prediction of preeclampsia have been evaluated in recent studies.[9-11] Generally, first trimester and second-trimester biochemical or biophysical parameters for predicting early-onset pre-eclampsia were found to be more sensitive and specific than those for late-onset preeclampsia.[12-16]

To date, no marker has demonstrated a high level of accuracy for use in clinical practice. However, because of the heterogeneous nature of pre-eclampsia, we thought that a combination of 2 or more independent biochemical markers, each reflecting a different pathophysiological process, should potentially increase the likelihood of deriving appropriate prediction algorithms. Therefore, the current study analyzed the predictive value of prenatal screening test biomarkers in preeclampsia and compared these biomarker levels between uncomplicated and preeclamptic pregnancies to identify high-risk groups.

METHODS

Approval was obtained from the institutional review board. The records of consecutive patients diagnosed with pre-eclampsia and who gave birth between January 2013-December 2016 were reviewed retrospectively. Pre-eclampsia patients with the first trimester combined and second trimester triple screening tests were included in the study. Patients who had high risk in aneuploidy screening tests and who had insufficient records were excluded. Also, patients with chronic diseases like diabetes mellitus, and endocrine disorders like hypo/hyperthyroidy were excluded.

Patients' age, body mass index (BMI), last menstruation date, systemic, gynecological and obstetric history, clinical symptoms at admission to hospital, laboratory and ultrasonography findings, treatment practices during hospitalization were recorded. Smoking status, medical history and recent history of pre-eclampsia were also recorded. As for the first trimester screening test, nuchal translucency (NT) MoM, pregnancy-associated plasma protein-A (PAPP-A) multiples of median (MoM), free beta (human chorionic gonadotropin) hCG MoM levels were recorded. And as for the second trimester screening test, hCG MoM, alpha fetoprotein (AFP) MoM and unconjugated estriol (UE3) MoM levels were recorded. All sonography scans were carried out by expert obstetricians. NT was measured in the midsagittal plane while the fetus was in the neutral position. Calipers were placed on the inner borders of the nuchal line. The widest space of the NT was obtained. The obstetric outcomes of the patients and newborns (type of delivery, birth weight, week of birth, Apgar scores and neonatal intensive care unit (NICU) admission) were also recorded. The presence of proteinuria, 24-hour urine results, platelet counts, blood urea nitrogen (BUN), creatinine, aminotransferase levels were also noted.

The diagnosis and classification of preeclampsia was made as per the American College of Obstetricians and Gynecologists criteria.[17] Patients were grouped as mild or severe. Severe preeclampsia was defined as blood pressure ≥160/110 mmHg, proteinuria ≥5 g/d, or maternal symptoms (epigastric pain), signs of end-organ dysfunction, abnormality of laboratory tests (platelet count less than 100000/microliter, blood levels of liver transaminases to twice the normal concentration, elevated serum creatinin >1.1 mg/dL). Patients who had blood pressure less than 160/110 mmHg with no adverse conditions as defined above were accepted as having mild pre-eclampsia. Early-onset preeclampsia was pre-eclampsia occurring under 34 weeks of pregnancy. While 85 pregnant women diagnosed with pre-eclampsia were defined as the study group, the control group patients were defined as consecutive patients who gave birth in the same hospital with no

additional obstetric problems having results of aneuploidy screening test results.

Statistical Analysis

Data were analyzed via Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). The conformity of the data to the normal distribution was analyzed using the Kolmogorov-Smirnov test and Shapiro-Wilk test. While parametrical methods were used in the analysis of variables with a normal distribution, non-parametric methods were used for variables that do not have a normal distribution. To compare two independent groups with each Independent-samples t-test and Mann-Whitney U test were used. Categorical data comparison was tested with Pearson chi-square and Fisher exact tests.

In multivariate analysis, independent predictors of preeclampsia were examined using logistic regression analysis using possible factors identified in previous analysis. Hosmer-Lemeshow test was used for the model fit. Data were examined at 95% confidence level and p value less than 0.05 was accepted as significant.

RESULTS

This study was conducted on 178 women. While 85 pre-eclamptic patients formed the study group, 93 pregnant women formed the control group. Of the 85 preeclamptic pregnant patients, 32 of them had mild preeclampsia, 53 of them had severe pre-eclampsia.

The mean age, BMI, aminotransferase, BUN, creatinine was higher in the preeclampsia group. Furthermore, NICU admission of the newborns was higher in the preeclampsia group and the birth weight of newborns in the preeclampsia group was lower. However, there was no significant difference between the groups regarding platelet count, parity, smoking status and in vitro fertilization (IVF) status (Table 1).

The first trimester and second trimester screening test results of the groups are shown in Table 2. There were statistically significant differences in terms of NT MoM, PAPP-A MoM levels between the groups (p=0.003, p=0.040 respectively). While the mean biochemical hCG MoM value of patients preeclampsia was 1.4±1.1, it was 0.9±0.4 in the control group (p<0.0001). However, no significant difference regarding AFP and UE3 values were found (Table 2).

A comparison of demographic, laboratory data and newborn outcomes of mild preeclamptic and severe preeclamptic patients is shown in Table 3. There were statisticaly significant difference between the groups' aspartate aminotransferase (AST), BUN levels and gestational age of the pregnancy. Additionally, birth weight of the newborns of severe preeclampsia patients was lower than those mild preeclampsia patients.

When the mild preeclamptic patients were compared with the control patients, we found statisticaly significant difference between the groups' age, gestation age, BMI,

Table 1. Demographic, andropometric, clinical characterictics and newborn characteristics of patients

Variable	Preeclampsia (n=85)	Controls (n=93)	p
Age (year)	30.5±6.7	26.1±5.3	**<0.0001**
Gestational age (week)	34.5±4.4	38.6±2.1	**<0.0001**
BMI (kg/m^2)	31.8±6.2	28.9±4.4	**0.001**
Nulliparity	42 (49.4%)	45 (48.4%)	0.891
Smoking status	12 (14.1%)	13 (14%)	0.979
IVF status	2 (2.4%)	0	0.227
ALT (U/L)	36.2±80.5	16.1±3.6	**<0.0001**
AST (U/L)	39.5±118.3	10.9±3.6	**<0.0001**
BUN (mg/dL)	21.4±8.8	15.6±4.6	**<0.0001**
Creatinine (mg/dL)	1.4±7.8	0.5±0.08	**<0.0001**
Platelet count	229847.0±67420.7	239279.5±59602.0	0.457
Systole/diastole >3	6 (7.1%)	0	**0.002**
End diastolic flow loss	10 (11.7%)	0	**0.003**
NICU admission	32 (37.6%)	2 (2.2%)	**<0.0001**
Birth weight (gr)	2398.6±1077.3	3294.3±443.8	**<0.0001**

Values were given as means±standard deviation, number (%).

p<0.05 was considered statistically significant.

BMI: Body mass index, IVF: In vitro fertilization, NICU: Neonatal intensive care unit, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen

AST and creatinine levels. Furthermore, birth weight of patients with mild preeclampsia was found to be lower (p=0.012) (Table 4).

A ROC curve was drawn to show the predictive role of NT MoM and hCG MoM for preeclampsia. The area under the curve (AUC) was 0.628±0.042 [p=0.003; 95% confidence interval (CI): 0.545-0.711] for NT MoM and hCG MoM 0.697±0.047 (p<0.001; 95% CI: 0.605-0.789). The AUC was 0.589±0.044 (p=0.040; 95% CI: 0.503-0.676) for PAPP-A MoM. This result indicates a significant relationship between preeclampsia and these variables. For predicting best calculated cut-off NT MoM value for predicting preeclampsia was 0.77, with a sensitivity of 67% and specificity of 52% and of hCG MoM was 1.09 with a sensitivity of 67% and specificity of 67%. First and second trimester screening test biomarkers in the prediction of preeclampsia using logistic regression analysis were shown in Table 5.

DISCUSSION

In this study, we determined the predictive value of first and second trimester screening test biomarkers. We found that low levels of PAPP-A MoM, high levels of hCG, MoM and NT MoM were useful significant predictive markers for the prediction of preeclampsia. This finding of the current study confirm the previous studies indicating that low levels of maternal serum PAPP-A levels were associated with preeclampsia.[18,19] However, when we evaluated pre-

Table 2. First trimester and second trimester screening test results of the groups

	Preeclampsia (n=85)	Controls (n=93)	p
NT MoM	0.9±0.2	0.7±0.1	**0.003**
PAPP-A MoM	1.13±0.90	1.14±0. 52	**0.040**
Free beta-hCG MoM	1.4±1.5	1.1±0.6	0.417
Second trimester hCG MoM	1.4±1.1	0.9±0.4	**<0.0001**
AFP MoM	1.1±0.7	0.9±0.4	0.103
UE3 MoM	0.9±0.3	0.9±0.3	0.905

Values were given as means±standard deviation. p<0.05 was considered statistically significant.

NT: Nuchal translucency, MoM: Multiples of median, PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin, AFP: Alpha fetoprotein, UE3: Unconjugated estriol

Table 3. Comparison of demographic, laboratory data and newborn outcomes of mild preeclamptic and severe preeclamptic patient

	Mild preeclampsia (n=32)	Severe preeclampsia (n=53)	p
Age (year)	31.5±6.3	29.9±7.0	0.266
Gestational age (week)	35.9±3.9	33.6±4.5	**0.010**
BMI (kg/m^2)	31.7±6.1	32±6.3	0.982
NT MoM	0.8±0.2	0.9±0.2	0.123
PAPP-A MoM	1.0±0.6	1.1±1	0.789
Free beta-hCG MoM	1.7±2.2	1.3±0.8	0.989
hCG MoM	1.3±1.0	1.6±1.1	0.147
AFP MoM	1.0±0.4	1.2±0.8	0.657
UE3 MoM	0.9±0.2	0.9±0.3	0.425
ALT (U/L)	18.8±7.1	46.8±100.7	0.063
AST (U/L)	13.0±4.7	55.5±148.0	**0.047**
BUN (mg/dL)	17.6±6.2	23.7±9.5	**0.002**
Creatinine (mg/dL)	2.8±12.7	0.6±0.1	0.109
Birth weight (gr)	2804.0±987.3	2153.9±1063.8	**0.004**

BMI: Body mass index, NT: Nuchal translucency, MoM: Multiples of median, PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin, AFP: Alpha fetoprotein, UE3: Unconjugated estriol, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen.

Values were given as means±standard deviation. p<0.05 was considered statistically significant.

eclampsia as mild and severe preeclampsia, we found no statistically significant difference between the groups as to PAPP-A levels.

NT, is one of the most important ultrasonographic markers that is used to determine the risk of chromosomal anomalies and adverse pregnancy outcomes. NT, which was measured as a part of the first trimester screening test, was higher in the preeclampsia group in the current study. To show the predictive role of NT MoM we drew a ROC curve. The AUC was 0.628±0.042 (p=0.003; 95% CI: 0.545-0.711). According to logistic regression analysis, an increase in NT MoM increased the risk of preeclampsia 10 times and we concluded that the increase in NT MoM is an effective parameter in differentiating pregnant women who will develop pre-eclampsia. In a study, the association between fetal NT and gestational hypertension and preeclampsia was evaluated. Correlation analysis demonstrated that NT MoM level was positively correlated with maternal diastolic blood pressure at admission time for delivery. According to this study, the placental pathological changes could have been the reason for developing pregnancy-associated hypertension may also affect the NT thickness.[20]

Moreover, the second trimester elevated beta-hCG levels have been shown to be associated with adverse pregnancy outcomes such as preeclampsia similar to our study. It was shown that mid-trimester hCG levels were significantly correlated with pre-eclampsia severity. In this study, a prediction model to identify women at risk early on for severe pre-eclampsia development has been suggested with a sensitivity of 70% and specificity of 71%.[21] Also, it was concluded that the combination of PAPP-A and the high second trimester hCG correlated with the development of pre-eclampsia.[12] The best calculated cut-off value of hCG MoM for predicting preeclampsia was 1.09 with a sensitivity of 67% and specificity of 67% in our study. We found that an increase in hCG increases the risk of preeclampsia 2.5

Table 4. Comparison of demographic, laboratory data and newborn outcomes of mild preeclacmptic and control group patients

	Mild preeclampsia (n=32)	Controls (n=93)	p
Age (year)	31.5±6.3	26.1±5.3	**<0.0001**
Gestational age (week)	35.9±3.9	38.6±2.1	**<0.0001**
BMI (kg/m^2)	31.7±6.1	28.9±4.4	**0.018**
NT MoM	0.8±0.2	0.7±0.1	0.285
PAPP-A MoM	1.0±0.6	1.1±0.5	0.127
hCG MoM	1.3±1.0	0.9±0.4	0.53
ALT (U/L)	18.8±7.1	16.1±3.6	0.078
AST (U/L)	13.0±4.7	10.9±3.6	**0.020**
BUN (mg/dL)	17.6±6.2	15.6±4.6	0.129
Creatinine (mg/dL)	2.8±12.7	0.5±0.08	**0.012**
Birth weight (gr)	2804.0±987.3	3294.3±443.8	**0.012**

BMI: Body mass index, NT: Nuchal translucency, MoM: Multiples of median, PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin, AFP: Alpha fetoprotein, UE3: Unconjugated estriol, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen.

Values were given as means±standard deviation. p<0.05 was considered statistically significant.

Table 5. First and second trimester screening test biomarkers in the prediction of preeclampsia using logistic regression analysis

	Relative risk	p	Confidence interval 95%
NT MoM	10.8	0.003	2.3-51.5
PAPP-A MoM	1.1	0.57	0.7-1.9
Free beta-hCG MoM	0.9	0.95	0.62-1.5
Total hCG MoM	2.5	0.007	1.2-5.2
AFP MoM	1.1	0.68	0.5-2.3
UE3 MoM	0.8	0.66	0.3-2

NT: Nuchal translucency, MoM: Multiples of median, PAPP-A: Pregnancy-associated plasma protein A, hCG: Human chorionic gonadotropin, AFP: Alpha fetoprotein, UE3: Unconjugated estriol

times. Preeclampsia is a trophoblastic disease and since hCG is released from the trophoblast, therefore the serum hCG concentration in patients with pre-eclampsia may be altered.

Besides these results, when the preeclampsia group was evaluated separately as mild and severe preeclampsia, we found no statistically significant difference. We found that the first trimester and second trimester biomarkers did not show a significant difference in distinguishing the severity of preeclampsia.

Considering that the preeclamptic patient group was terminated earlier due to maternal morbidity and mortality, it was an expected result that the gestational age at birth was lower in this group. Again, it is was expected to result that in the preeclampsia group the birth weights were lower and admission to NICU was higher. Furthermore, as for the laboratory findings of the patients, AST, alanine aminotransferase, BUN and creatinine levels, which are among the preeclampsia diagnostic criteria, were found to be higher in the preeclampsia group.

The risk factors for preeclampsia were nulliparity, maternal age of more than 35 years, conception by assisted reproductive technology, prepregnancy BMI of more than 30 kg/m^2.[22] In accordance with this study, BMI was higher in our preeclampsia group. However, there was no statistically significant difference between the groups as to IVF status and nulliparity. This result may be because there were only 2 patients to be conceived by IVF in our study.

The strength of our study is that the examinations were performed by expert obstetricians who had finished the same education process. The patients were analyzed in 3 groups as mild preeclampsia, severe pre-eclampsia and control groups. And regarding our knowledge, there is no previous study for predicting preeclampsia examining both the first trimester screening the test and the second trimester screening test of the same patient in the literature.

Study Limitations

However, we have some limitations. This was a retrospective study with a relatively small number of patients. Furthermore, mean arterial pressure (MAP) was shown to be associated with preeclampsia.[23] But in our study, it was not recorded as a study parameter at the time of admission for the first trimester screening test. Whether further investigations could be done using a combination of these first trimester and second trimester screening test results combined by ultrasonography and MAP remains to be seen.

CONCLUSION

In conclusion, low levels of PAPP-A MoM, high levels of hCG MoM and NT MoM are useful significant predictive markers for prediction of preeclampsia. However, these markers have not been found to be clinically useful for the mild preeclampsia group compared with the severe preeclampsia group in terms of distinguishing from the normotensive group. Moreover, for the severe preeclampsia group, increased NT MoM and hCG MoM values were found to be significant markers in predicting pre-eclampsia, Although they are unideal markers with low sensitivity and spesifity, we believe that a better prediction of preeclampsia by evaluating these markers together with pre-eclampsia clinical risk factors can be provided.

Ethics

Ethics Committee Approval: The study were approved by the Zekai Tahir Burak Women Health Care Training and Research Hospital of Local Ethics Committee (protocol number: 16, date: 11.09.2017).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.T., Concept: B.T., S.K., Design: D.T.E., Data Collection or Processing: Z.A.Y., D.T.E., Analysis or Interpretation: D.T.E., S.K., Literature Search: Z.A.Y., B.T., Writing: Z.A.Y., D.T.E.

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