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The role of measuring PAPP-A and placental volume for the prediction of preeclampsia at 11-14 weeks of gestation

Öznur Dündar[1], Yusuf Olgaç[1], Deniz Acar[2], Ali Ekiz[2], Gökhan Yıldırım[2], Ali Gedikbaşı[2]

[1]Clinics of Obstetrics & Gynecology, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey
[2]Perinatology Department, Clinics of Obstetrics & Gynecology, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

Abstract

Objective: The purpose of this study was to analyze the role of PAPP-A and placental volume measured between 11+0 and 13+6 weeks of gestation on the subsequent development of preeclampsia, and to determine the presence of any statistical difference.

Methods: Placental volume and serum PAPP-A were measured on 740 pregnant women who referred to our hospital for routine care at 11+0 to 13+6 weeks of gestation. Antenatal care was successfully continued in 502 cases until delivery.

Results: While 460 cases out of 502 cases who gave birth were not affected by preeclampsia, 18 of them were diagnosed with early preeclampsia before 34 weeks of gestation, and 24 of them with the late preeclampsia at or after 34 weeks of gestation as resulting with delivery. Mean placental volume was higher in the late preeclampsia group ($p<0.01$) and in the unaffected group ($p<0.001$) compared to the early preeclampsia group. There was no significant difference between the late preeclampsia group and the unaffected group in terms of the placental volume values. PAPP-A MoM values were higher in the late preeclampsia group ($p<0.05$) and the unaffected group ($p<0.001$) than the early preeclampsia group. There was no significant difference between the late preeclampsia group and the unaffected group in terms of the PAPP-A values.

Conclusion: Mean PAPP-A and placental volume values were found significantly lower in preeclampsia group than unaffected group. Yet, it is difficult to provide prediction of preeclampsia only by using these two parameters according to the literature data. It may be helpful to obtain successful results for preeclampsia prediction by adding other factors associated with patient as well as PAPP-A and placental volume findings.

Key words: Preeclampsia prediction, PAPP-A, placental volume.

11-14 hafta PAPP-A ve plasental volüm ölçümlerinin preeklampsi öngörüsündeki yeri

Amaç: Çalışmanın amacı 11+0 ile 13+6 gebelik haftaları arasında ölçülen düşük PAPP-A ve plasenta volümünün, preeklampsi gelişimindeki öngörüsünü ortaya koymak ve istatistiksel olarak bir fark olup olmadığını saptamaktır.

Yöntem: Gebeliğinin 11+0 ile 13+6 haftalarında rutin kontrol için hastanemize başvuran 740 gebenin, PAPP-A ve plasenta volümü değerleri ölçüldü. Beş yüz iki olgunun antenatal takipleri doğuma kadar başarı ile tamamlandı.

Bulgular: Gebeliğini tamamlayan 502 olgunun 460'ı preeklampsiden etkilenmezken, 18'i gebeliğin 34. haftasından önce (erken preeklampsi), 24'ü ise 34. haftasında veya daha sonra (geç preeklampsi) doğumla sonuçlanacak şekilde preeklampsi tanısı aldılar. Geç preeklampsi grubunda ($p<0.01$) ve etkilenmemiş grupta ($p<0.001$) plasenta volümü ortalaması erken preeklampsili gruptan anlamlı olarak daha yüksekti. Geç preeklampsi ile etkilenmemiş grubun plasenta volümü değerleri arasında anlamlı farklılık yoktu. PAPP-A MoM değerleri, geç preeklampsi grubunda ($p<0.05$) ve etkilenmemiş grupta ($p<0.001$), erken preeklampsili gruptan anlamlı olarak daha yüksekti. Geç preeklampsi ile etkilenmemiş grubun PAPP-A değerleri arasında anlamlı farklılık yoktu

Sonuç: Çalışmamızda ortalama PAPP-A ve plasenta volümü ölçümleri preeklampsi grubunda, etkilenmemiş gruba göre anlamlı derecede daha düşük saptandı. Bununla birlikte literatür verileri doğrultusunda preeklampsi öngörüsünde yalnızca bu iki parametrenin kullanımı ile öngörü sağlamak güçtür. PAPP-A ve plasenta volümü bulgularının dışında hasta ile ilişkili diğer faktörlerin eklenmesi, preeklampsi öngörüsünde daha başarılı sonuçlar sağlamamızda yararlı olabilir.

Anahtar sözcükler: Preeklampsi öngörüsü, PAPP-A, plasenta volümü.

Correspondence: Öznur Dündar, MD. Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, İstanbul, Turkey.
e-mail: ozgurdundar72@yahoo.com

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Introduction

The incidence rate of preeclampsia during pregnancy is 3-4%, and it is one of the major reasons for maternal and fetal morbidity and mortality in underdeveloped and developing countries.[1] Preeclampsia and gestational hypertension (GH) develop in about 8-10% of primigravidas. Despite the wide researches, the etiopathology of preeclampsia has not been enlightened yet.[2]

In the studies for the etiopathogenesis of preeclampsia, many ideas were suggested such as increased pressor responses, prostaglandins, endothelins, genetic predisposition, immunologic factors, inflammatory factors and endothelium cell activation. The most commonly accepted one among these theories is thromboxane-prostacycline imbalance as well as maternal immune system defect and/or genetic predisposition.[1] Insufficient trophoblastic invasion on spiral arteries causes common system endothelium damage and consequently the preeclampsia with abnormal placentation. Therefore, high diastolic resistance and decreased placental perfusion in diastolic uteroplacental circulation, and non-increase of uteroplacental blood flow which is expected to increase 10 times during pregnancy cause maternal fetal circulation to be affected negatively. Placental defects occur during 10 to 16 weeks of gestation, and clinical symptoms and findings appear generally at 2nd and 3rd trimesters.[1]

Active screening for trisomy 21, 13 and 18 is performed by using free β-hCG in metarnal serum and PAPP-A levels together with maternal age and fetal nuchal translucency (NT) at 11+0 and 13+6 weeks of gestation. Pathologic clinical cases are associated with changes in these values. Each measured value must certainly and be converted to MoM (multiples of median) value first according to gestational age, maternal age, race, smoking habit, conception method, gestation number and devices and markers used.[3] There are evidences that low maternal serum PAPP-A values in pregnancies which are chromosomally normal have high risks of developing preeclampsia at subsequent periods.[4] However, using PAPP-A value during preeclampsia screening is not an efficient method, because only 8-23% of affected cases are below 5th percentile, which is 0.4 MoM.[5] The effective first trimester screening for preeclampsia can be performed together with placental volume measurement by 3D ultrasonography (3D US), PAPP-A, characteristics of pregnant, body mass index (BMI) and ethnical characteristics.[6]

The aim of our study was to analyze the relationship between preeclampsia development and placental volume measured by 3D US and maternal serum PAPP-A measured at 11+0 and 13+6 weeks of gestation.

Methods

This study was carried during antenatal follow-up of 740 cases admitted to the perinatology unit of our hospital for first trimester screening test between February 2010 and March 2011. The cases were informed about the study and their informed consents were obtained. Our study was initiated with the decision no 245 dated June 12th, 2009 of the Ethics Committee of our hospital.

First application evaluations were conducted between 11+0 and 13+6 weeks of gestation. Their detailed medical histories including information such as age, BMI, delivery number, medical background (preeclampsia history, diabetes mellitus, chronic hypertension, thrombophilia, antiphospholipid syndrome etc.), medication history (anti-hypertensives, thyroxine, steroids, insulin, betamimetics, aspirin, anti-coagulants, anti-epileptics, anti-depressants, anti-thyroids, thyroxine, anti-inflammatories), and conception methods (spontaneous, ovulation induction, IVF).

Measured PAPP-A concentrations were converted to MoM value by correcting according to CRL, weight of pregnant, race, pregnancy number, smoking habit and conception method.

Transabdominal ultrasonography was performed in order to determine major fetal anomalies by CRL, placental volume and NT measurements (GE Healthcare, Milwaukee, WI, USA; Voluson 730 Expert, 4-dimensional transabdominal 2.5-7.5 mHz convex probe was used); in retroverted cases, transvaginal probe was used for patients who were obese and when the quality was insufficient. Volumetric measurements were done by virtual organ computer-aided analysis (VOCAL).

Curved angle was adjusted to 85°, thus probe was made to be vertical to the placental plane. Placental volume was measured by VOCAL software in the system of ultrasonography device by obtaining 12 individual placental sections through 15°. Parallel sections were obtained from one end to other end of placenta. The margins of each 12 placental sections were drawn manually or with the help of automatic movements of transducer by considering to distinguish the uterine wall (which is usually stays under the placenta as a thin layer at this week of gestation). At the end of twelve measure-

ments, the device was displaying the volume and 3D placental view. Measurement of one placental volume took about 2 minutes. All measurements were carried out by one of two authors (ÖD, YO).

Results of placental volume were not provided to the cases or their physicians for not influencing the type of gestational management. PAPP-A MoM values, sonography findings, characteristics of cases and their medical data were recorded to the computer database. Antenatal follow-ups of the cases were maintained in our perinatology polyclinic. Data of pregnancy results were obtained from obstetric records in our hospital. All reported obstetric results or pregnancy-associated hypertensions were researched in order to determine any preeclampsia case.

Pre-eclampsia is defined by the International Society for the Study of Hypertension in Pregnancy as gestational hypertension above 90 mmHg on two separate occasions 4 hours apart accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine or proteinuria of +2 on dipstick after 20 weeks of gestation in a previously normotensive woman, and applied according to this definition

Statistical Analysis

The cases were separated into three groups as early preeclampsia, late preeclampsia and unaffected according to their obstetric results. The distribution of data was tested by Kolmogorov-Smirnov. ANOVA was used for the analysis of parametric discrete data, and Mann-Whitney for the analysis of non-parametric data. By using Mann-Whitney U test, PAPP-A and placental volume mean MoM values were compared according to the obstetric results. The distinction of early preeclampsia from unaffected group and the distinction of late preeclampsia from unaffected group were done by ROC curve.

Regression analyses were carried out in order to determine which characteristics of cases, placental volume and PAPP-A MoM values significantly contribute to predict preeclampsia. SPSS 19.0 (SPSS Inc., Chicago, IL, USA) software was used for analyses.

Results

The first trimester screening test was performed on 740 live singleton pregnancies applied at 11+0 and 13+6 weeks of gestation. The obstetric results of 227 cases could not be accessed, so they were excluded. Six cases were excluded due to fetal anomaly and 5 cases due to fetal death or abortus before 24 weeks of gestation. In 460 out of 502 cases did not develop preeclampsia while 18 cases developed hypertension before 34 weeks of gestation (early preeclampsia), and 24 cases developed hypertension after 34 weeks of gestation (late preeclampsia), and they were diagnosed as preeclampsia.

There was no significant difference among patients according to their preeclampsia type in terms of their ages, BMI, parity presence, parity number, crown-rump

Table 1. Distribution of patient-associated variables according to preeclampsia type (Kruskal-Wallis / Mann-Whitney U test / ANOVA / chi-square test / Fisher's exact test).

	Clinical condition / Preeclampsia type		
	Unaffected Mean±SD / n (%)	Late preeclampsia Mean±SD / n (%)	Early preeclampsia Mean±SD / n (%)
Age	28.08±5.19	28.25±5.91	28.33±6.93
BMI	23.98±4.75	24.91±4.95	23.62±3.61
Parity number	0.9±1.09	0.88±1.12	1.11±1.02
Weeks of gestation according to CRL	12.38±1.2	12.4±0.73	12.38±0.63
Conception type			
Spontaneous	449 (97.9%)	24 (100%)	18 (100%)
Ovulation induction	8 (1.7%)	0	0
IVF	2 (0.4%)	0	0
Free β-hCG value (MoM)	1.16±0.69	0.97±0.5	1.1±0.52
Smoking habit	63 (13.8%)	4 (%16.7)	5 (27.8%)
Preeclampsia history	14 (3.1%)	**3 (12.5%)***	2 (11.1%)

*Statistically significant with unaffected group, p<0.05.

Table 2. Comparison of placental volume with PAPP-A values according to preeclampsia type (Kruskal-Wallis / Mann-Whitney U test.)

	Clinical condition / Preeclampsia type			
	Unaffected Mean±SD	Late preeclampsia Mean±SD	Early preeclampsia Mean±SD	p value
Placental volume (mL)	69.4±23.2*	58.2±24.2†	34.7±14.7	**0.000**
PAPP-A (MoM)	0.9±0.51*	0.74±0.94‡	0.29±0.15	**0.000**

When compared with early preeclampsia: *p<0.001, †p<0.01, ‡p<0.05

length, conception type, free β-hCG MoM value, smoking habit, and fetal loss rates (p>0.05). Preeclampsia history rate of late preeclampsia group (n=3; 12.5%) was compared with unaffected group (n=14; 3.1%), and no statistical significance was found (p<0.05) (**Table 1**).

When placental volumes were compared with early preeclampsia group (34.7±14.7 mL), it was significantly higher in late preeclampsia group (58.2±24.2 mL; p<0.01), and unaffected group (69.4±23.2 mL; p<0.001). No statistical significance was found in the comparison between late preeclampsia group and unaffected group (p>0.05) (**Table 2**).

Mean PAPP-A MoM value was significantly higher in late preeclampsia group (0.74±0.94; p<0.05) and unaffected group (0.90±0.51; p<0.001) compared to early preeclampsia group (0.29±0.15). There was no significant difference between late preeclampsia group and unaffected group in terms of PAPP-A values (p>0.05) (**Table 2**).

In order to determine the threshold value in the relationship between placental volume and early preeclampsia, we checked the impact level by ROC curve. According to sensitivity of the area under curve, the most ideal threshold value was 36 mL. In patients with 0-36 mL placental volume, the sensitivity to detect early preeclampsia was 61.1%. The specificity of placental volume above 36 mL was found as 96.7% for unaffected group, and as 79.2% for late preeclampsia group (**Table 3**). According to this result, the possibility for early preeclampsia in patients with 0-36 mL placental volume (odds ratio, OR) was 46.1 times higher (15.79 – 136.43) than unaffected group (**Table 3**). The possibility to have early preeclampsia for patients within same placental volume range was found as 5.97 times (1.52-23.43) compared to late preeclampsia group (**Table 3**). The possibility to have late preeclampsia for patients within same placental volume range was found as 7.77 times (2.56-23.62) compared to unaffected group (**Table 3**).

Accurate prediction average was found as 96.9% in the logistic model established for the distinction with PAPP-A between the early preeclampsia group and the unaffected group. While the accuracy was 99.8% for the prediction of the unaffected group, it was as low as

Table 3. The relationship between placental volume and preeclampsia type.

		Clinical condition / Preeclampsia type		
		Unaffected n (%)	Late preeclampsia n (%)	Early preeclampsia n (%)
Placental volume	0-36 ml	15 (3.3%)	5 (20.8%)	11 (61.1%)
	>36 ml	443 (96.7%)	19 (79.2%)	7 (38.9%)
		Odds	**Minimum**	**Maximum**
Placental volume 0-36 ml	Early preeclampsia / Unaffected	46.41	15.79	136.43
	Late preeclampsia / Unaffected	7.77	2.56	23.62
	Early preeclampsia / Late preeclampsia	5.97	1.52	23.43

22.2% for the prediction of the early preeclampsia. Consequently, PAPP-A was considered as a variable which may be effective for predicting that patient would not have preeclampsia.

Accurate prediction average was found as 97.1% in the logistic model established for the distinction with placental volume between the early preeclampsia group and the unaffected group. While the accuracy was 99.3% for the prediction of the unaffected group, it was as low as 38.9% for the prediction of the early preeclampsia. Consequently, placental volume was considered as a variable which may be effective for predicting that patient would not have preeclampsia.

Accurate prediction average was found as 96.8% in the logistic model established for the distinction with placental volume and PAPP-A between the early preeclampsia group and the unaffected group. While the accuracy was 98.9% for the prediction of the unaffected group, it was 44.4% for the prediction of the early preeclampsia. Consequently, placental volume and PAPP-A were considered together as variables which may be effective for predicting that patient would not have preeclampsia (**Table 4**).

Discussion

Placental sizes in preeclamptic pregnants were found significantly smaller than those of normotensive pregnants. Placental/fetal weight rates decreased in these cases. While the incidence rate of infarction in placenta is 33% in mild preeclampsia, it is 60% in severe preeclampsia. In patients with severe preeclampsia, common infarction areas are seen in about 30% of cases while retroplacental hematoma is seen in 12-15% of them.[2]

Together with the use of devices that can perform volumetric measurement by 3D ultrasonography, it has become possible to measure placental volume precisely. Hafner et al. reported that there is a close relationship between midtrimester placental volume and delivery birth.[7] In their study, Hafner et al. measured placental volume in 1st trimester by 3D ultrasonography and found that placental volume being less than expected was associated with preeclampsia, intrauterine growth retardation (IUGR), and being small for gestational age (SGA).[8] In our study, the results were found to be consistent with the studies performed on the same subject. While mean birth weight was found significantly higher in late preeclampsia group and unaffected group compared to early preeclampsia group, it was significantly higher in unaffected group than late preeclampsia group.

In the study of Schuchter et al. (2001), placental volume was measured in 380 singleton pregnants between 11 and 14 weeks of gestation. It was found that the sensitivity and false positivity values for predicting complications such as preeclampsia, IUGR and ablatio placentae was 22% and 9%, respectively, by detecting placental volume below 10th percentile.[9] Hafner et al. measured placental volume between 11 and 14 weeks of gestation in 2489 singleton pregnancies with low risk, and found that the sensitivity and specificity for predicting preeclampsia were 38.5% and 90%, respectively, when volume was <10th percentile.[8]

In the study performed by Rizzo et al., uterine artery Doppler evaluation and measurement of placental volume were carried out at the same time in 348 nullipara pregnants between 11 and 14 weeks of gestation, and it was seen that mean placental volume in pregnants developing preeclampsia (4.1%) was found to be less than

Table 4. Accuracy of prediction according to preeclampsia type by using placental volume and PAPP-A values (logistic regression).

		OR within 95% confidence interval			
	β	Odds	Minimum	Maximum	p value
Placental volume	-0.066	1068	1025	1113	0.002
PAPP-A	11.816	135.368.5	461	39.702.884	0.000
Constant value	-5.474	0.004			0.000
Accuracy of prediction, %	General				96.8%
	Early preeclampsia				44.4%
	Unaffected				98.9%

normotensive group statistically. The authors reported the sensitivity of placental volume measurement and uterine artery Doppler examination for predicting preeclampsia as 50% and 56%, respectively. It was shown that the sensitivity for predicting preeclampsia increased to 68.7% when placental volume and uterine artery Doppler were used together.[10]

Sancak measured placental volume of 336 singleton pregnants between 11 and 14 weeks of gestation in a low-risk population during the thesis study performed in Zeynep Kamil Maternity and Children Diseases Training and Research Hospital, found 10th percentile limit value of placental volume as 43 cm^3 and analysis was carried out according to these values. It was shown in the same study that approximately 45.94% of cases developing preeclampsia were below 10th percentile, and mean placental volume was found to be statistically and significantly low in cases with preeclampsia compared to normotensive cases. Placental volume was found to be above 10th percentile in 54.06% of cases preeclampsia. In the study, the sensitivity, specificity, positive and negative predictive values of placental volume measurement for predicting preeclampsia were found as 45.94%, 90.63%, 37.77%, and 93.13%, respectively.[11]

The findings in our study are consistent with the previous studies reporting decreased PAPP-A levels in serum at 11+0 and 13+6 weeks of gestation of pregnants developing preeclampsia. One of the additional findings of our study is the lower PAPP-A levels in early preeclampsia group than the late preeclampsia group.

Ong et al. analyzed the relationship between first trimester maternal serum PAPP-A level and gestational complications in 5297 pregnants (of which 80 were preeclamptic); and concluded that PAPP-A and free β-hCG was significantly lower in the preeclamptic group compared to the control group, and that PAPP-A was below the 5th percentile in 10% of preeclamptic pregnants and free β-hCG was below 5th percentile in 7% of them. They considered that low free β-hCG levels were associated with insufficient trophoblastic invasion and small placental mass.[5]

Yaron et al. analyzed 1622 pregnants (of which 27 were preeclamptic); and found that PAPP-A value being below 0.25 MoM resulted relative risk to be 6.09 for preeclampsia.[6] Smith et al. conducted their study totally on 8839 pregnants (of which 331 were preeclamptic), and similar to our study, they found that PAPP-A value was significantly low in the preeclamptic group compared to the control group, and free β-hCG value made no significant difference among two groups. They also detected that preeclampsia risk was increasing in pregnants who had PAPP-A value below 5th percentile (OR=2.3 [1.6-3.3]).[12]

Dugoff et al. analyzed 34271 pregnants (of which 764 were preeclamptic) in their FASTER study in terms the relationship between the gestational complications and the markers of first trimester screening test, and found OR as 1.54 (95% confidence interval [1.16-2.03]), and preeclampsia detection rate as 7.85% when threshold value of PAPP-A was considered as 0.42 MoM (5th percentile).[13]

The biochemical markers of first trimester screening test were compared between 222 preeclamptic pregnant women and 47,770 control cases in the study of Spencer et al., and it was found, similar to our study, that PAPP-A measurement was significantly low in study group. When threshold value was considered as 0.41 MoM (5th percentile) for PAPP-A, OR value was found as 3.7 (95% confidence interval [2.3-4.8]), and preeclampsia detection rate as 14.6%.[14]

Again, in the thesis study conducted by Ersan Önal, 298 singleton pregnancies with low risk were analyzed and perinatal clinical outcomes of 85 patients with PAPP-A value less than 0.49 MoM were researched. It was stated that low PAPP-A values were statistically significant in terms of especially IUGR, preeclampsia, preterm labor and both SGA and the condition of being large for gestational age (LGA).[15] In our study, mean PAPP-A value was significantly higher in the late preeclampsia group and the unaffected group than the early preeclampsia group, and there was no significant difference between the late preeclampsia group and the unaffected group in terms of PAPP-A values. Therefore, it was considered that the PAPP-A value was a significant method to distinguish the early preeclampsia group from the unaffected group and to distinguish the early preeclampsia group from the late preeclampsia group.

Accurate prediction average was found as 96.9% in the logistic model established for the distinction with PAPP-A between the early preeclampsia group and the unaffected group. While the accuracy was 99.8% for the prediction of the unaffected group, it was as low as 22.2% for the prediction of the early preeclampsia. Consequently, PAPP-A was considered as a variable which may be effective for predicting that patient would not have preeclampsia.

Also, according to our data, preeclampsia risk specific to patient associated with PAPP-A is affected strongly by the characteristics of pregnant woman. For instance, while early preeclampsia risk with a PAPP-A value at 0.1 MoM is 5% for a white nullipara woman, it increases to 21% with the preeclampsia history in previous pregnancy. The formulas obtained by regression analyses were used for these calculations.

Accurate prediction average was found as 96.8% in the logistic model established for the distinction with placental volume and PAPP-A between the early preeclampsia group and the unaffected group. While the accuracy was 98.9% for the prediction of the unaffected group, it was 44.4% for the prediction of the early preeclampsia. Consequently, placental volume and PAPP-A were considered together as successful for predicting that patient would not have preeclampsia, in other words they have high negative predictive values; however, they are both insufficient to distinguish the population that would have preeclampsia.

Conclusion

Consequently, placental volume and PAPP-A are not sufficient to predict both preeclampsia and non-preeclampsia groups; it is required to use variables depending on mother such as birth weight and weeks of gestation. In this way, positive predictive value increases and results of our study become more meaningful.

Conflicts of Interest: No conflicts declared.

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