

The Role of Placental Elastography in Predicting PAPP-A Levels: An Observational Cross-sectional Study

PAPP-A Düzeylerinin Tahmininde Plasental Elastografinin Rolü: Gözlemsel Kesitsel Bir Çalışma

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Abstract

Objective: Pregnancy-associated plasma protein A (PAPP-A) is synthesized by placental trophoblastic tissues. Sonoelastography is a non-invasive ultrasonographic technique for assessing tissue stiffness. Studies have recently highlighted the clinical significance of evaluating placental elasticity to determine its function in obstetrics. Thus, the present study examines whether placental elastography can detect pathological changes in placental tissue linked to serum PAPP-A levels.

Methods: In an observational cross-sectional study, we evaluated 200 pregnant women at 10-14 weeks' gestation and performed ultrasound elastography examinations of the placenta. Serum PAPP-A levels (mIU/L) and nuchal translucency thickness (mm) were recorded. Correlation analysis was performed to assess the relationship between placental elastography-placental strain ratio (PSR) values and PAPP-A levels.

Results: The patients' median age was 29 years [interquartile range (IQR), 17-42]. Median values were: the crown-rump length, 59.1 (IQR 45-84) mm; nuchal thickness, 1.0 (IQR 0.47-2.0) mm; and PAPP-A, 0.96 (IQR) mIU/L. No significant correlation was found between PSR value and PAPP-A ($\rho=-0.118$, $p=0.104$).

Conclusion: In the correlation analysis, we could not find a statistically significant association between placental elastography PSR values and PAPP-A. According to the first-trimester combined test results, only 3 of our patients were in the high-risk group. We used strain elastography software. Nevertheless, shear-wave elastography may yield more sensitive results. These could be limitations of our study and possible reasons why we did not detect a significant relationship.

Keywords: Pregnancy-associated plasma protein A, placental strain elastography, ultrasound

Öz

Amaç: Gebelikle ilişkili plazma proteini A (PAPP-A), plasental trofoblastik dokular tarafından sentezlenir. Sonoelastografi, doku sertliğini non-invaziv ultrasonografi kullanarak teşhis etmek için kullanılan bir tekniktir. Son zamanlarda yapılan çalışmalarda plasentanın elastikiyetinin değerlendirilmesinin doğumdaki işlevini belirlemede klinik önemi vurgulanmıştır. Bu nedenle, bu çalışmada plasental elastografinin serum PAPP-A düzeyi ile ilişkili plasenta dokusundaki patolojik değişiklikleri tespit edip edemeyeceği araştırılmıştır.



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Öz

Yöntem: Gözlemsel kesitsel bir çalışmada, 10-14. gebelik haftalarında 200 gebe kadın değerlendirildi ve plasentaya ultrasonografi-elastografi incelemesi yapıldı. Serum PAPP-A düzeyleri (mIU/L) ve ense kalınlığı (mm) kaydedildi. Plasental elastografi-plasental gerinim oranı (PSR) değerleri ile PAPP-A düzeyleri arasında korelasyon analizi yapıldı.

Bulgular: Hastaların yaş medyanı 29 [çeyrekler arası aralık (ÇAA), 17-42] yılı. Baş-popo mesafesinin ortalama değeri 59,1 (ÇAA 45-84) mm, NT 1,0 (ÇAA 0,47-2,0) mm ve PAPP-A 0,96 (ÇAA) mIU/L olarak bulundu. PSR değeri ile PAPP-A arasında anlamlı bir korelasyon bulunmadı ($\rho = -0,118$ $p = 0,104$).

Sonuç: Korelasyon analizinde plasental elastografi PSR değerleri ile PAPP-A arasında istatistiksel olarak anlamlı bir korelasyon bulamadık. Birinci trimester kombine test sonuçlarına göre hastalarımızın sadece 3'ü yüksek risk grubundaydı ve strain elastografi yazılımını kullandık. Yine de, shear-wave elastografisi daha hassas sonuçlar verebilir. Bunlar çalışmamızın kısıtlılıkları olabilir ve anlamlı bir ilişki bulamamamızın olası nedenleridir.

Anahtar Kelimeler: Gebelik ilişkili plazma proteini A, plasental elastografi, ultrason

Introduction

Pregnancy-associated plasma protein A (PAPP-A) is synthesized by placental trophoblastic tissue and is detected in maternal serum⁽¹⁾. It is most commonly used as a component of the combined first-trimester test for Down syndrome screening. It is detected at low levels in trisomies 21, 18, and 13^(2,3). Moreover, many studies have described its relationship with undesirable complications caused by abnormal placentation, such as preterm delivery, intrauterine growth retardation (IUGR), preeclampsia (PE), miscarriage, stillbirth, and placenta accreta⁽⁴⁻⁷⁾.

PAPP-A in maternal serum is primarily produced and released by the syncytiotrophoblast⁽⁸⁾. Various studies indicate that alterations in placental tissues are linked to PAPP-A levels. The findings reveal a marked decrease in the size of terminal villi in pregnancies with reduced PAPP-A levels and fetal growth restriction compared to a control group with average PAPP-A levels and uncomplicated pregnancies⁽⁹⁾. This is a crucial indication that should not be overlooked. Placental pathology has been associated with non-optimal first-trimester secretion of the analyte PAPP-A in pregnancies with adverse outcomes, particularly PE⁽¹⁰⁾. Also, in pregnancies affected by T21, there is a notable presence of both fetal structural abnormalities, which manifest as various physical malformations, and placental developmental defects, which can compromise the vital functions of the placenta and impact the well-being of the fetus. Histopathological evaluations of placentas affected by T21 reveal striking characteristics: pronounced enlargement, asymmetry, and disordered arrangement of chorionic villi. These marked abnormalities underscore the profound effects of the condition on placental structure and function⁽¹¹⁾. In addition, recent studies have revealed that

abnormalities in trophoblast fusion and differentiation can significantly affect placental development. These defects lead to a higher proportion of trophoblasts displaying a double-layered structure, which can disrupt normal placental function. Additionally, an increased number of villous capillaries may contribute to altered blood flow and nutrient exchange in the placenta. This atypical vascularization may have implications for fetal growth and overall pregnancy outcomes⁽¹¹⁾.

Sonoelastography is a technique for diagnosing tissue stiffness using non-invasive ultrasonography⁽¹²⁾. This method is commonly employed to evaluate the biomechanical alterations in affected parenchymal tissue^(12,13). Studies have recently highlighted the clinical significance of evaluating placental elasticity to determine its function in obstetrics⁽¹⁴⁻¹⁶⁾. Thus, the present study examines whether placental elastography, a non-invasive functional method, can detect pathological changes in placental tissue linked to the serum PAPP-A level. Our goal was to establish the association between serum PAPP-A levels and placental elastography values.

Materials and Methods

This study was reviewed and approved by the İzmir Katip Çelebi University Clinical Research Ethics Committee (approval no: 16, date: 23.02.2023). The study was conducted in accordance with the principles outlined in the Helsinki Declaration. To ensure compliance, all patients provided signed consent forms.

Our study was conducted prospectively as an observational cross-sectional study. We did not enroll patients with pre-existing systemic diseases, such as diabetes mellitus, hypertension, cardiac conditions, or thyroid conditions.

However, we included all other pregnant women who voluntarily agreed to participate in the study.

A power analysis for binary logistic regression determined that the minimum sample size was 192 individuals. In this case, the power of the test is expected to be approximately 80.1%. We evaluated the first 200 pregnant women at 10-14 weeks of gestation who applied to our hospital and consented to participate in the study between February 23 to April 30, 2023, consecutively.

We employed the Esaote MyLabSeven real-time tissue elastography software and an 8-1 MHz multi-frequency AC2541 probe for placental assessment during a routine first-trimester fetal ultrasound evaluation. The medical practitioner employed the ultrasound probe to apply and release pressure on the tissue during the placental elastography examination, thereby compressing and decompressing it. The compression process ensures that the transducer optimizes the machine's color coding.

Tissue elasticity was represented on the screen by a color scale (red, yellow, green, and blue). Red indicates the lowest elasticity, whereas blue indicates the highest. A total of 4 regions of interest (ROIs), each with an area of 31.89 mm², were determined. One area (A, circle Z1) was located in the myometrium, and 3 areas (B, circles Z2, Z3, and Z4) were located in the placenta. When choosing ROIs, we selected areas with homogeneous distributions of blue, green, and red colors. The device automatically calculated the ratios of elasticity among these four areas (Elx1, Elx2, Elx3, and Elx4) and determined the SR values (Elx2/Elx1=SR1, Elx3/Elx1=SR2, and Elx4/Elx1=SR3) (Figure 1). We have defined the placental strain ratio (PSR) as the average strain ratio (SR1+SR2+SR3)/3.

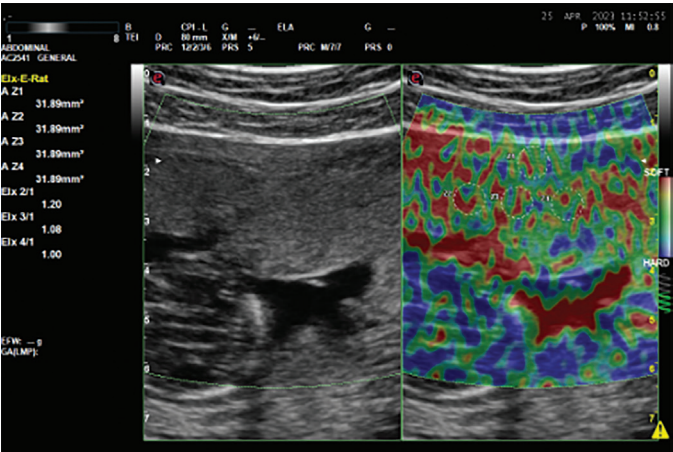


Figure 1. Ultrasound image of placental sonoelastography

Measurements were taken three separate times by two different blinded researchers and averaged to avoid potential bias.

The first-trimester combined test results, serum PAPP-A levels (mIU/L), and nuchal translucency (NT) thickness (mm) were extracted from our hospital's patient records.

Statistical Analysis

We used SPSS software (version 23.0) (IBM Corp., Armonk, N.Y., USA) also known as the Statistical Package for the Social Sciences. The Kolmogorov-Smirnov test was used to assess the normality of the distributions. Correlation analysis between placental elastography-placental ratio (PSR) values and PAPP-A levels was performed to evaluate the extent to which PSR reflected PAPP-A values. We examined the correlation between placental elastography values and PAPP-A values using Spearman correlation analysis and determined the correlation coefficient (rho). If the p-value was less than 0.05, it was considered statistically significant.

Results

The patients' ages ranged from 17 to 42 years, with a median age of 29 years. The crown-rump length (CRL) at the time of the first-trimester combined testing was 59.1 mm (45-84 mm); NT was 1.0 mm (0.47-2.0 mm); and PAPP-A had a median of 0.96 mIU/L (Table 1). The first-trimester combined test results for 3 patients indicated high risk (trisomy 21 risks were 1:42, 1/131, and 1/135, respectively). The risk of trisomy 21 for 12 pregnant women was 1/250-1/1000, while the remaining pregnant women were in the low-risk range (1/1216-1/99000).

Amniocentesis was performed on the pregnant woman with a risk of 1/42, and the result indicated a normal karyotype.

Table 1. Demographic variables	
Variables	Data
Demographic variables (n=200)	
Age (year), median (IQR)	29 (8)
Gravida, median (IQR)	2 (2)
Parity, median (IQR)	1 (1)
CRL (mm), median (IQR)	59.1 (12.4)
NT (mm), median (IQR)	1.0 (0.2)
PAPP-A (mIU/L), median (IQR)	0.96 (0.77)
Placental strain ratio (PSR), median (IQR)	0.79 (0.79)
CRL: Crown-rump length, NT: Nuchal thickness, PAPP-A: Pregnancy-associated plasma protein A, IQR: Interquartile range	

The other two refused to undergo an invasive procedure, but no anomalies were detected on second-trimester ultrasound examinations in any of our patients.

PAPP-A levels ranged from 0.17 to 6.9 mIU/L, with a median of 0.96 mIU/L. The values of PSR varied from 0.6 to 1.5, with a median of 0.79 (Figure 2).

Correlation analysis revealed no notable correlation between the PSR value measured by placental elastography and PAPP-A. ($\rho = -0.118$ $p = 0.104$) (Table 2).

Discussion

Pregnancy complications can cause fetal and maternal morbidities, so finding the causes of these complications and detecting them early have always been focuses of attention among researchers. Many parameters have been scrutinized in this regard. One of them is the maternal serum PAPP-A level. Many studies have evaluated the relationship between PAPP-A levels and pregnancy complications, such as preterm delivery, IUGR, PE, miscarriage, and stillbirth⁽⁴⁻⁷⁾.

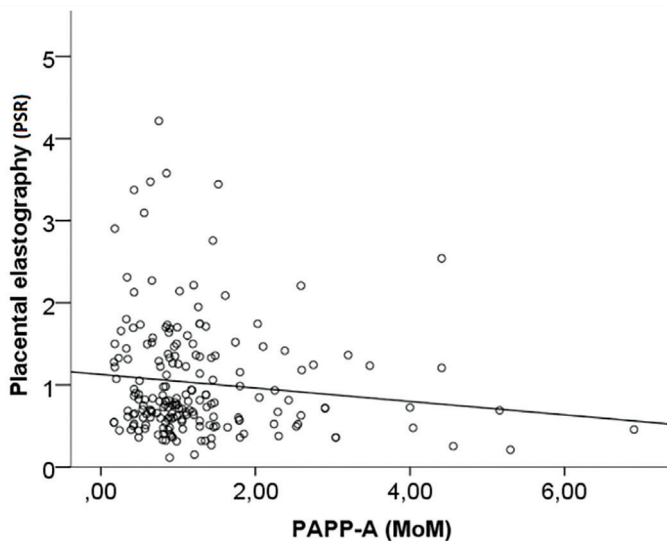


Figure 2. Correlation of PAPP-A and PSR

PAPP-A: Pregnancy-associated plasma protein A, PSR: Placenta strain ratio, MoM: Multiples of the median

Table 2. Correlation analysis of PAPP-A with PSR value

Variables	ρ	p-value
PAPP-A	-0.118	0.104

ρ : Spearman's rank correlation coefficient, PAPP-A: Pregnancy-associated plasma protein A, PSR: Placenta strain ratio

Rojas-Rodriguez et al.⁽¹⁶⁾ stated that PAPP-A is a metalloprotease secreted by the placenta and modulates the bioavailability of insulin-like growth factor (IGF) through proteolysis of IGF-binding proteins (IGFBPs) 2, 4, and 5. The researchers discovered that mice lacking PAPP-A exhibited conditions similar to those observed in humans with gestational diabetes mellitus, such as adipose tissue restructuring, pregnancy-induced insulin resistance, and fatty liver disease⁽¹⁷⁾.

Boutin et al.⁽¹⁷⁾ conducted a study to assess how well PAPP-A can predict placental outcomes in low-risk nulliparous pregnancies. PAPP-A is moderately associated with PE [with an area under the curve (AUC) of 0.57 and a 95% confidence interval (CI) of 0.53-0.61] and with small-for-gestational-age infants (with an AUC of 0.62 and a 95% CI: of 0.56-0.69). However, fetal death was not associated with PAPP-A (with an AUC of 0.43 and a 95% CI: of 0.23-0.63)⁽¹⁸⁾. Odibo et al.⁽⁹⁾ found significant differences in first-trimester PAPP-A levels of pregnant women who experienced PE, growth restriction, or preterm delivery later in their pregnancy. Kapustin et al.⁽¹⁸⁾ evaluated PAPP-A and fb-hCG values in the first-trimester of pregnancies complicated by diabetes to assess their ability to predict potential obstetrical complications such as macrosomia, PE, IUGR, and preterm birth. Compared with the control group, PAPP-A and fb-hCG MoM levels were significantly lower in the 5-10% range and notably higher in the 95% range⁽¹⁹⁾.

PAPP-A has been investigated in various components of the fetoplacental unit because of its association with adverse obstetric outcomes. For instance, *in vitro* study, Kavoussi et al.⁽¹⁹⁾ assessed the presence of PAPP-A in blastocoel-fluid-conditioned media obtained from IVF/ICSI patients. They detected PAPP-A mRNA in 56.3% of samples⁽²⁰⁾.

Because PAPP-A is a placenta-derived hormone, researchers have also focused on placental pathology. In another study, Odibo et al.⁽¹⁰⁾ discovered noteworthy variations in PAPP-A, ADAM12, and placental growth factor levels in cases of PE, premature delivery, and small-for-gestational-age infants with specific placental histological findings. Their study provided evidence linking placental pathology and inadequate secretion of analytes during the first-trimester to unfavorable outcomes, particularly PE⁽¹⁰⁾. However, pathological examination of the placenta cannot be used as a predictor during pregnancy, since it is typically performed after delivery. Therefore, the researchers aimed to predict the relationship between different ultrasound

measurements, PAPP-A levels, and indirect pregnancy complications.

Various ultrasound measurements have been examined to predict PAPP-A levels and, thus, associated complications. Wortelboer et al.⁽²⁰⁾ measured uterine artery impedance by transvaginal Doppler ultrasound and evaluated its relationship with the PAPP-A level. They concluded that the increase in these hormone levels was negatively correlated with uterine artery impedance⁽²¹⁾. Another study investigated the correlation between placental volume and PAPP-A levels and reported that PAPP-A levels were closely associated with placental size up to 8 weeks. This relationship disappeared after the luteoplacental shift at 8 weeks⁽²²⁾.

Papastefanou et al.⁽²²⁾ evaluated the correlation between PAPP-A and first-trimester fetal ultrasound parameters, including dCRL, fetal heart rate (dFHR), and dNT. They found that PAPP-A had a direct correlation with dNT and an inverse correlation with dCRL and dFHR. The statistical analysis revealed a significant difference between the observed and adjusted MoM, with a p-value of less than 0.001⁽²³⁾.

Our objective was to establish a conclusive link between PAPP-A levels and placental elastography, a non-invasive ultrasound method that can indirectly indicate pathological changes in the placenta by assessing tissue stiffness. To our knowledge, this is the first study using such an approach. Generally, studies on ultrasound elastography have focused on the pathology of tissues, such as the thyroid and breast^(24,25). However, recent ultrasound elastography studies have also focused on pregnant women to investigate pregnancy complications such as pregnancy-induced hypertension, PE, and IUGR⁽²⁶⁻²⁹⁾. According to a literature review by Edwards et al.⁽²⁵⁾, studies have shown a correlation between PSR values and pregnancy complications. Ultrasound elastography can provide a quantitative evaluation of the placenta's biomechanical characteristics when its function is affected⁽²⁵⁾.

The association of first-trimester placental biomarkers with adverse pregnancy outcomes continues to attract researchers' attention. This recent study once again highlighted that when combinations of biomarkers were assessed, PAPP-A and AFP were independently associated with small-for-gestational-age, and that PAPP-A alone was associated with pre-eclampsia and preterm birth⁽²⁹⁾.

Study Limitations

Our correlation analysis did not reveal a meaningful association between placental elastography PSR values and PAPP-A. According to the first-trimester combined test results, only 3 of our patients were in the high-risk group. This could be a limitation of our study and a possible reason why we did not find a significant relationship. We also performed ultrasonography in the first-trimester, but PSR values may differ in the third trimester. This timing limitation must be considered in our study. Lastly, we used strain elastography software, but shear-wave elastography may yield more sensitive measurements.

PAPP-A has been the subject of studies since the 1970s, when it was first defined. Its new functions are still being determined, and research on it has continued for 50 years⁽¹⁾. Future studies are likely to reveal findings elucidating the mechanisms of PAPP-A.

Conclusion

Correlation analysis revealed no statistically significant association between placental elastography PSR values and PAPP-A levels. A potential limitation of our study is the small number of high-risk cases identified based on the first-trimester combined test, as only three patients fell into this category. Furthermore, the use of strain elastography software may have contributed to the lack of significant findings, as shear-wave elastography could yield more precise and sensitive results. These factors may collectively explain the absence of a significant correlation.

In prospective studies involving larger patient cohorts, second- and third-trimester elastography examinations could be included, which might lead to more definitive conclusions regarding the PAPP-A level and the prediction of pregnancy complications. We believe that our study may prompt further research.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the İzmir Katip Çelebi University Clinical Research Ethics Committee (approval no: 16, date: 23.02.2023).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practises: H.Ş.S., Ç.S., Concept: H.Ş.S., M.Ş., Design: Y.A., Ç.S., Data Collection or Processing: H.Ş.S., Ç.S., Analysis or Interpretation: H.Ş.S., M.Ş., Literature Search: M.Ş., Ç.S., Writing: H.Ş.S., Y.A.

Conflict of Interest: The authors declare no conflict of interest.

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