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Elevated first-trimester PAPP-A is a marker in high-risk pregnancies with an increased risk of placenta accreta in predicting adverse outcomes

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Abstract. – OBJECTIVE: Our work aims to determine whether there is an association between first-trimester serum pregnancy-associated plasma protein A (PAPP-A) multiples of the median (MoM) value and placenta previa with or without placenta accreta spectrum disorders (PAS) in women.

PATIENTS AND METHODS: A retrospective analysis was performed on 267 patients who had first-trimester screening test results for aneuploidy, including nonadherent placenta previa (n=106), placenta previa with PAS (n=60), and control group (healthy pregnant women with previous cesarean section and normal placental location, n=101). To assess the significant difference between these groups, PAPP-A MoMs were compared.

RESULTS: The median PAPP-A MoM of 1.96 in placenta previa with PAS was significant (>0.88) in nonadherent placenta previa and 0.89 in the control group ($p<0.001$). Serum PAPP-A was found to be significantly associated with the severity of bleeding, such that patients with severe bleeding of 1,500 mL or more (n=54) had a higher mean PAPP-A MoM (1.93±0.69; $p<0.001$). Furthermore, the mean PAPP-A MoM was found to be 1.96±0.74 in the hysterectomy group and 0.89±0.47 in the conservative management group, and the difference was found to be significantly higher ($p<0.001$).

CONCLUSIONS: Elevated PAPP-A values in the first trimester of pregnancy may be a useful marker for identifying women at higher risk of PAS and adverse outcomes.

Key Words:
High risk, Low income, PAPP-A, PAS, Placenta previa.

Introduction

In 1937, Irving[1] reported a cohort of 18 cases in which the placenta failed to detach from the underlying uterine wall after delivery and first described what is now known as the morbidly adherent placenta. Since then, the incidence of PAS has increased, with an increasing number of cases reported worldwide ranging from 0.01% to 0.1% of live births[2].

Placental implantation occurs by the 10th week of gestation, and cases of accreta have been reported[3] as early as the first trimester. Prenatal detection and risk stratification for PAS is primarily performed by ultrasound[4], although another diagnostic method, MRI, has been proposed[5] as a complementary or alternative method, having high sensitivity and specificity for detecting PAS. Many patients have limited access to prenatal screening at high-risk prenatal diagnostic centers, and although ultrasound and MRI have undoubtedly improved prenatal diagnosis, between half and two-thirds of cases remain undiagnosed, leading to worse maternal outcomes[6]. These pregnancies have serious adverse outcomes that primarily include complications due to surgical attempts to control maternal hemorrhage, including but not limited to the need for cesarean hysterectomy, disseminated intravascular coagulation, massive transfusion of blood products, sepsis, and injury to surrounding organs[7], with mortality rates as high as 7% in some regions[8]. Previous studies[9,10] have shown that the introduction of a standardized approach to the management of women with suspected PAS by a dedicated multidisciplinary team has shown promising results in improving maternal outcomes compared with standard obstetric care, such as reducing the likelihood of early morbidity (prolonged admission to the maternal intensive care unit, massive blood transfusion, coagulopathy, ureteral injury, or early reoperation). It has also been observed[11] that referral to a multidisciplinary hospital for women undergoing peripartum hysterectomy has also been shown to reduce maternal mortality by up to 70%.

The development of non-invasive and convenient diagnostic methods, such as serum analysis, could greatly improve the ability to detect and

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diagnose PAS early in pregnancy, allowing for better planning and management of the condition. PAPP-A (pregnancy-associated plasma protein-A) is a maternal serum marker used in the first-trimester screening test for aneuploidy. Zinc metalloproteinase produced by placental syncytiotrophoblasts and decidua is secreted into the maternal circulation in increasing concentrations until delivery. Although its function is not well understood, it is generally accepted that PAPP-A is responsible for the proteolysis of insulin-like growth factor (IGF) from IGF-binding protein-4 (IGFBP-4), a role in placental growth and in the regulation of trophoblast invasion[12]. Low PAPP-A levels have been associated[13,14] with an increased risk of developing preeclampsia, low birth weight, pregnancy loss, and preterm birth, all of which are associated with abnormal trophoblast invasion and placental development. The aim of this study was to investigate the potential utility of the first-trimester serum PAPP-A as a marker of placental invasion and its potential impact on the early detection and management of PAS disorders.

Patients and Methods

The study population included pregnant women who were admitted to the Department of Perinatology at the University of Health Sciences Etlik Zübeyde Hanım Gynecology Training and Research Hospital with the diagnosis of placenta previa and placenta previa with PAS and delivered between January 2018 and October 2022. In the cohort, patients who had first-trimester screening test results were included in the study. The Institutional Review Board of the hospital approved the study protocol (Ref. 2022/77). This retrospective chart review, including patient demographic and obstetric characteristics, maternal and neonatal outcomes, was conducted using surgical and pregnancy-related records in the hospital's patient record system. Patients with placenta previa and PAS were presented according to histopathological findings for those who underwent hysterectomy and according to surgical records for those who were managed conservatively. Patients were divided into three groups: placenta previa with PAS, nonadherent placenta previa (PP), and control (healthy pregnant women with previous cesarean section and normal placental location). Maternal serum PAPP-A levels were measured using an automated instrument (IMMULITE 2000 Immunoassay System, Siemens, USA) as part of the routine first-trimester antenatal screening program for aneuploidy between 11+0 and 13+6 weeks' gestation. Weeks of gestation were determined from the last menstrual period or first-trimester CRL (crown-rump length) measurement. PAPP-A data were calculated as MOM and adjusted for gestational age, maternal weight, smoking status, and preexisting diabetes. Exclusion criteria included pregnant women with missing clinical and delivery data, twin or multiple pregnancies, fetal chromosomal abnormalities, miscarriages or stillbirths, and missing or outlier data for PAPP-A MoM.

Statistical Analysis

Results were analyzed using the Statistical Package for the Social Sciences, version 28.0 (IBM Corp., Armonk, NY, USA). The study used mean±(standard deviation) or median±(minimum-maximum) to describe numerical data. The Shapiro-Wilk test was used to test the normality of continuous variables. Significant statistical differences in the means of variables between groups were examined using Student's *t*-test, Mann-Whitney U, or one-way ANOVA test. Furthermore, the Chi-square test was used to determine the significance of ordinary and severity. The confidence interval was 95%, and $p<0.05$ was considered a statistically significant difference between groups.

Results

A total of 267 patients were included in the study: 60 in the PAS group, 106 in the PP group, and 101 in the control group, matched for age and body mass index. The clinical data of the patients, including PAPP-A MoM values, are shown in Table I. There were no statistically significant differences in age, BMI, and gestational age at blood sampling. Gestational age at delivery was significantly lower in the PAS group compared with the control group ($p<0.001$). Note that the birth weights corresponded to the gestational age at delivery, and none of the newborns were growth restricted. The history of previous cesarean sections was found to be significantly higher in the PAS group ($p=0.028$). In addition, blood transfusion and cesarean hysterectomy were statistically significant in the PAS group ($p<0.001$). The median PAPP-A MoM in the PAS group was 1.96 MoM, 0.88 MoM in the PP group, and 0.89 MoM in the control group. The difference

Table I. Comparison of demographic features and clinical characteristics.

Characteristics	Group 1 Placenta previa with PAS (n=60)	Group 2 Placenta previa without PAS (n=106)	Group 3 Healty pregnant control group (n=101)	p^1	p^2
Age (years), mean±sd	33.03±5.65	32.47±5.87	33.1±7.27	*p* (1-2)=ns *p* (1-3)=ns *p* (2-3)=ns	0.307
BMI (kg/m^2), mean±sd	28.34±3.93	28.08±3.84	27.96±4.03	*p* (1-2)=ns *p* (1-3)=ns *p* (2-3)=ns	0.270
Smoking, n (%)	2 (3.3)	3 (2.8)	3 (2.9)	*p* (1-2)=ns *p* (1-3)=ns *p* (2-3)=ns	0.439
Gestational week at blood sampling, mean±sd	12.38±0.25	12.34±0.24	12.23±0.21	*p* (1-2)=ns *p* (1-3)=ns *p* (2-3)=ns	0.168
Delivery gestational week, mean±sd	32.7±3.2	35.6±3.32	37. ±2.41	*p* (1-2)<0.001 *p* (1-3)<0.001 *p* (2-3)<0.001	<0.001
Management, n (%) (cesarean hysterectomy at delivery)	54 (90)	11 (10.3)	0	<0.001	
Previous cesarean section, mean±sd	1.91±1.33	1.20±1.37	0.8±0.94	*p* (1-2)=0.034 *p* (1-3)<0.001 *p* (2-3)=0.045	0.028
Birth weight (gr), mean±sd	2,436.78±560.18	2,473.44±595.54	3,058.42±273.05	*p* (1-2)=ns *p* (1-3)<0.001 *p* (2-3)<0.001	<0.001
Blood transfusion, n (%) PAPP-A MoM, median (min-max)	60 (100) 1.96 (0.2-4.9)	70 (66) 0.88 (0.3-3.1)	3 (2.9) 0.89 (0.2-2.9)	<0.001 *p* (1-2)<0.001 *p* (1-3)<0.001 *p* (2-3)=ns	<0.001

BMI; body mass index, PAPP-A; pregnancy-associated plasma protein-A. p^1: between groups, p^2: within groups. ns; not significant, $p<0.05$ statistically significant.

between the groups was statistically significant ($p<0.001$). To further investigate the possible relationship between the PAPP-A MoM value and the severity of hemorrhage, the patients in the study were divided into three subgroups based on the amount of blood loss during delivery (Table II). The subgroups were: Group 1: patients without hemorrhage (n=168), Group 2: patients with hemorrhage but with an estimated volume lower than 1,500 mL (n=45), and Group 3: patients with severe hemorrhage with an estimated volume of 1,500 mL or more (n=54). Mean PAPP-A MoM (0.97±0.46, 1.25±0.71, and 1.93±0.69, respectively) and a significant correlation were found between blood loss volume and PAPP-A MoM values ($p<0.001$). In addition to the overall analysis, patients in the study were divided into two subgroups based on treatment approach: the hysterectomy group (n=60) and the conservative management group (n=207), as shown in Table III. The hysterectomy group had a median PAPP-A MoM of 1.96 compared to 0.89 in the conservative management group and was statistically significant ($p<0.001$).

Table II. Comparison of PAPP-A MoM values for different severity of hemorrhage.

	Non-bleeding (n=168)	Estimated blood loss <1,500 ml (n=45)	Estimated blood loss >1,500 ml (n=54)	p^1	p^2
PAPP-A MoM (mean±sd)	0.97±0.46	1.25±0.71	1.9 ±0.69	p (1-2) <0.001 p (1-3) <0.001 p (2-3) <0.001	0.001

p^1: between groups, p^2: within groups. PAPP-A=pregnancy associated plasma protein-A. $p<0.05$ statistically significant.

Table III. Comparison of PAPP-A MoM values between cesarean hysterectomy and conservative management group.

	Cesarean hysterectomy at delivery (n=60)	Conservative management at delivery (n=207)	p
PAPP-A MoM (mean±sd)	1.96±0.74	0.89±0.47	<0.001

PAPP-A=pregnancy associated plasma protein-A. Results were analyzed by independent samples *t*-test. $p<0.05$ statistically significant.

Discussion

The incidence of PAS has increased over the last few decades, mainly due to the worldwide increase in cesarean section rates[15]. This trend has also been observed[16-19] in Turkey, where the cesarean section rate has gradually increased over the years. Data analysis from the Turkey Demographic and Health Survey[16] showed a steady increase in the cesarean section rate, from 13.9% in 1998 to 21.2% in 2003, 37% in 2008, 48.0% in 2013, and 52% in 2018. Previous studies[17] have shown that women with a history of cesarean section have the highest risk of developing PAS. In our study, the likelihood of having PAS was significantly higher in the group with a previous cesarean section. The prenatal diagnosis of PAS is essential to reduce the risk of maternal complications, including peripartum hemorrhage, blood transfusion, and hysterectomy. It allows multidisciplinary planning and referral to specialized centers, which can improve patient outcomes and reduce the need for intensive care admission[18,19].

PAS is a major challenge, but low-income countries such as Turkey face additional difficulties managing severe cases of PAS due to limited resources. Therefore, it is important to focus on developing cost-effective and widely accessible tools that can be used as a first step in identifying pregnant women at high risk for PAS. One possible approach is to use biochemical markers that are associated with adverse pregnancy outcomes, such as PAPP-A.

Several studies[20-23] have examined PAPP-A levels in the first trimester of pregnancies complicated by PAS. Desai et al[20] were the first to investigate the association between abnormal invasion and PAPP-A. They identified 16 cases of PAS with placenta previa and compared them with a control group of 82 women with nonadherent placenta previa. The median PAPP-A MoM in the PAS group was 1.68, which was significantly higher than 0.98 in the nonadherent placenta previa group. One of the main limitations of this study was the exclusion of conservatively managed cases of PAS. This exclusion might have influenced the results because conservatively managed cases are also part of PAS. In contrast, our study included both conservatively managed cases of PAS and cases that required hysterectomy. This approach allows for a more comprehensive analysis and consideration of the full spectrum of PAS management.

Thompson et al[21] analyzed a combined PAS dataset from London and New York to investigate potential differences in first-trimester maternal serum PAPP-A values between normal pregnancies, placenta previa, and PAS cases. The study included 516 participants, and the researchers found that PAPP-A levels were significantly elevated in cases of PAS (p=0.002). Buke et al[22] found that the median value of PAPP-A in the accreta group was 1.20 MoM, whereas it was 0.865 MoM in the non-accreta group (p=0.045).

Lyell et al[23] conducted a study of 37 cases of PAS and 699 cases of placenta previa to investigate the association between first-trimester PAPP-A levels and PAS. The researchers found that PAPP-A levels greater than 2.63 MoM were associated with a nearly ninefold increased risk

of PAS, independent from previous cesarean delivery. In addition, PAPP-A levels greater than 2.63 MoM were associated with a 23-fold and 36-fold risk of PAS associated with one and two previous cesarean deliveries, respectively. Despite the large population data set used in this study, an important limitation of this study was that the diagnosis of PAS was based on medical billing codes without surgical or pathologic confirmation. However, the study is quite powerful because of the large study population at the same time. The surgically and histopathologically confirmed diagnosis is the superiority of our study. Wang et al[24], in their study, found that the median PAPP-A MoM of placenta previa-accreta cases was 1.39, which was significantly higher than 0.98 in the control group (p<0.001). Similarly, we observed that the median PAPP-A MoM of 1.96 was significantly higher in the PAS group compared to 0.89 in the control group (p<0.001), but no significant difference was found between the PP and control groups.

In contrast to previous studies, the study by Penzhoyan et al[25] found no association between elevated PAPP-A levels and adverse pregnancy outcomes in patients with PAS. Nevertheless, a significant association was found between PAPP-A and the severity of blood loss in patients with PAS. In their study, PAPP-A MoM was 1.37±1.20 in the subgroup with blood loss lower than or equal to 1,000 mL (LBL) and 1.91±1.24 in the subgroup with blood loss greater than 1,000 mL (HBL) (p=0.025). In the present study, PAPP-A MoM was 1.93±0.69 in the subgroup with severe bleeding of 1,500 mL or more and 1.25±0.71 in the subgroup with bleeding less than 1,500 mL (p<0.001) and showed that first-trimester PAPP-A levels might be useful for early prediction of abnormal blood loss at delivery in pregnant women with PAS and for identifying a high-risk group for PAS. In the study by Thompson et al[21], PAPP-A levels tended to be higher in the hysterectomy group, but there was no statistically significant difference in PAPP-A levels between the hysterectomy and non-hysterectomy groups (p=0.10). Although Penzhoyan and Makukhina[25] found no significant association between PAPP-A levels and hysterectomy, the results of the study may have been influenced by the fact that the center where the study was conducted used temporary pelvic devascularization techniques instead of hysterectomy for the management of PAS. This may have affected the association between PAPP-A levels and the need for hysterectomy, since it represents a more definitive management option for severe cases of PAS. Contrary to these studies, the present study found that the mean PAPP-A MoM value was 1.96±0.74 in the hysterectomy group and 0.89±0.47 in the conservative management group (p<0.001).

Limitations

This study had some limitations. Because retrospective studies are useful for identifying associations between variables, they have limitations and cannot establish causality.

Conclusions

Elevated PAPP-A levels have been identified as a significant factor associated with an increased risk of placenta accreta and its associated complications, including massive peripartum hemorrhage and the need for hysterectomy. This association highlights the potential value of PAPP-A as an early diagnostic marker to guide multidisciplinary planning and appropriate management strategies. The integration of PAPP-A into clinical practice for managing high-risk pregnancies could have a significant impact on reducing maternal morbidity and mortality, particularly in low-income countries.

In conclusion, the integration of readily available and cost-effective tools, such as biochemical markers like PAPP-A, holds great promise for screening and management of placenta accreta, especially in resource-limited settings.

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Conflicts of Interest

The authors declare that they have no potential conflict of interest, including financial, personal, or other relationships with other individuals or organizations that could inappropriately influence or be perceived to influence the submitted work. The authors have no relevant financial or non-financial interests to disclose.

Authors' Contributions

G. Balkaş is the principal author of this study and designed the study, including resource acquisition, data collection and processing, data analysis and interpretation, writing-preparation of the original draft, and editing. Turhan Çaglar did the critical review and editing. Both authors have read and approved the final manuscript.

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Ethics Approval
Ethical approval was obtained from the local Ethics Committee at the Perinatology Clinic of the University of Health Sciences Etlik Zübeyde Hanım Gynaecology Training and Research Hospital (Reference: 2022/77).

Informed Consent
Not applicable, due to the retrospective nature of the study.

Availability of Data and Materials
Data and materials can be provided upon request to the corresponding author.

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