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ORIGINAL ARTICLE

Predictive value of first-trimester screening tests (PAPP-A and free βhCG) for placenta previa and placenta accreta spectrum disorders

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ABSTRACT

Objective: Placenta previa and the placenta accreta spectrum (PAS) represent critical conditions in pregnant women, carrying a life-threatening risk of bleeding and adverse obstetric outcomes. Timely diagnosis and intervention play a pivotal role in mitigating the potential risks associated with these conditions. Our study seeks to evaluate the significance of serum pregnancy-associated plasma protein-A (PAPP-A) and beta-human chorionic gonadotropin (βhCG) as early biomarkers for predicting placenta accreta spectrum disorders and placenta previa. This research is essential as further investigations are warranted to enhance our understanding of this significant medical condition.

Material and Methods: A retrospective study was carried out on 254 pregnant individuals with placenta previa who underwent cesarean section delivery at our hospital. Excluding 187 pregnant women who had placenta previa with or without placenta accreta spectrum but lacked PAPP-A and βhCG test results in the second trimester, the study focused on 30 cases of placenta previa with PAS, 37 cases of placenta previa without PAS, and 30 cases of body mass index (BMI)-matched healthy pregnant controls with available second-trimester test results. The comparison of PAPP-A and βhCG MoMs (Multiples of the Median) between these groups was conducted to assess significant differences.

Results: The ages of the individuals ranged from 22 to 41 years, with a mean of 32.29±4.14 years. BMI measurements ranged from 18 to 40 kg/m^2, with a mean of 26.22±4.48 kg/m^2. BMI, PAPP-A, and βhCG measurements did not show statistically significant differences between the groups ($p>0.05$). The mean age of the PAS group was significantly higher than that of the control group ($p<0.05$).

Conclusion: Our study did not find significant predictive value for PAPP-A and βhCG in placenta accreta spectrum. However, conflicting results from previous studies suggest the need for further research. Larger prospective studies are necessary to clarify the role of these biomarkers.

Keywords: Abnormally invasive placentation, free βhCG, placenta accreta spectrum, placenta previa, pregnancy-associated plasma protein-A.

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INTRODUCTION

The placenta accreta spectrum (PAS) represents a serious pregnancy disorder characterized by an abnormally firm attachment and deep infiltration of the placenta into the uterine layers.[1] Due to the increasing rates of cesarean sections (C/S) over the past two decades, the incidence of placenta accreta has increased approximately 13-fold.[2]

Clinically, PAS is associated with an increased risk of life-threatening maternal mortality, high rates of intrapartum hemorrhage, hysterectomy, blood transfusions, widespread coagulopathy, acute respiratory failure, renal failure, and postpartum hemorrhage.[3–5] While various surgical strategies can effectively minimize blood loss in the treatment of women diagnosed with PAS,[6] the key to successful management lies in the early identification of high-risk individuals.[7] Referral to a high-volume surgical center for women undergoing peripartum hysterectomy can also reduce maternal mortality rates by up to 70%.[8]

Preoperative management of PAS relies heavily on effective antenatal diagnosis, which typically involves the utilization of various imaging modalities. However, relying solely on radiological strategies, such as ultrasound technology and magnetic resonance imaging (MRI), may not be sufficient for accurate PAS diagnosis.[9] Also noteworthy is the observation that the sensitivity and specificity of these imaging techniques in detecting placenta accreta decrease significantly between the 15th and 20th weeks of gestation.[10] Therefore, the diagnosis of accreta necessitates a high-resolution setting and well-trained clinicians.[11]

Due to the ongoing debates regarding the reliability of currently available imaging modalities, the utilization of biomarkers has been proposed as an adjunct for the prediction of PAS risk. This approach is recommended because it offers several advantages, including convenience, repeatability, and ease of comparison.[12] For the purpose of validating a PAS diagnosis, several biomarkers, such as PAPP-A and βhCG, have been investigated for their usefulness in predicting PAS risk.[12–14]

The aim of our study was to evaluate the diagnostic value of serum PAPP-A and βhCG levels for the prediction of placenta accreta spectrum.

MATERIAL AND METHODS

The study cohort consisted of 254 pregnant women admitted to the Zeynep Kamil Maternity and Children Training and Research Hospital with a diagnosis of either placenta previa alone or placenta accreta concurrent with placenta previa and who had delivered between December 2015 and September 2021. Of these patients, only those with available first-trimester screening test results were included in the study. The patients were categorized into four groups: 1) placenta previa with PAS (PAS group), 2) placenta previa without PAS, 3) a control group consisting of healthy pregnant women with a history of previous cesarean section and normal placental location, and 4) a previa group that included all pregnant patients with placenta previa with and without PAS.

The first-trimester PAPP-A and BhCG MoM values were compared between these groups, particularly with the control group. The control group comprised patients who had undergone cesarean section after completing a 37-week pregnancy, were free of any diseases, and did not exhibit either previa or accreta.

Patients with placenta previa and coexisting accreta (PAS Group) were categorized based on histopathological examination results for those who had undergone hysterectomy or segmental resection and based on surgical records for those who were managed conservatively.

The Institutional Review Board of the Zeynep Kamil Maternity and Children Training and Research Hospital approved the study protocol. The study was conducted in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Demographic and obstetric data were gathered from the surgical and prenatal follow-up records within the patient database of Zeynep Kamil Maternity and Children Training and Research Hospital. These parameters included the gestational age at delivery, previous delivery mode, requirement for blood transfusion during cesarean section, and newborn birth weight.

The exclusion criteria included pregnant women without clinical and first-trimester screening test records and those with multiple pregnancies, fetal chromosomal abnormalities, miscarriages or stillbirths, and diagnoses of diabetes, hypertension, or preeclampsia.

Multiples of the median (MoM) values for βhCG and PAPP-A were extracted from first-trimester screening test reports. The maternal serum markers were measured using automated equipment (Clinical Laboratory Improvement Amendments CLIA kit). The MoM values of the markers were adjusted for gestational age, maternal weight, diabetes, and smoking status using logistic regression analysis.

Statistical Analysis

In the evaluation of the findings obtained in the study, IBM SPSS Statistics 22.0 software was utilized for statistical analysis. The normal distribution of parameters was assessed using the Kolmogorov-Smirnov test. For parameters demonstrating normal distribution, group comparisons were conducted using the One-Way ANOVA test, and the Post-Hoc Tukey HSD test was employed to identify the source of differences. Group comparisons of parameters not showing normal distribution were performed using the Kruskal-Wallis test. For comparisons between two groups of parameters demonstrating normal distribution, the Student's t-test was used, while the Mann-Whitney U test was employed for parameters not exhibiting normal distribution. The Chi-square test was used for the evaluation of qualitative data. Significance was evaluated at the $p<0.05$ level.

RESULTS

The study was conducted with a total of 97 cases: 30 were in the control group and 67 were in the previa group. All included patients were treated at our hospital between the years 2015 and 2021. The ages of the cases ranged from 22 to 41 years, with a mean age of 32.29±4.14 years. BMI measurements ranged from 18 to 40 kg/m², with a mean of 26.22±4.48 kg/m². No statistically significant differences were detected in BMI, PAPP-A, and fβhCG measurements between the groups ($p>0.05$) (Table 1).

The mean age was statistically significantly higher in the previa group than in the control group ($p<0.01$) (Table 1). The mean birth weight was statistically significantly higher in the control group than

Table 1: Evaluations according to groups

	Control (n=30)	Previa (n=67)	p
Age (years), Mean±SD	30.57±2.57	33.06±4.47	[1]0.001**
Body mass index (k/m^2), Mean±SD	25.34±3.95	26.64±0.69	[1]0.208
PAPP-A (MoM), Mean±SD (Median)	1.04±0.46 (1.01)	1.23±0.96 (0.99)	[2]0.785
βhCG (MoM), Mean±SD (Median)	0.96±0.43 (0.86)	1.17±0.75 (0.85)	[2]0.437
Birth weight (gram), Mean±SD	3173.33±420.63	2572.38±712.04	[1]0.001**
Gestational week at delivery, Mean±SD	38.20±1.27	34.62±3.44	[1]0.001**
Ceserean history, n (%)			[5]0.019*
0	8 (26.7)	31 (46.3)	
1	18 (60)	20 (29.9)	
≥2	4 (13.3)	16 (23.9)	
Blood transfusion, n (%)			[5]0.001**
–	30 (100)	35 (53)	
+	0 (0)	31 (47)	

1: Student t Test; 2: Mann-Whitney U test; 5Ki-Kare test; *: P<0.05; **: P<0.01; n: Number; PAPP-A: Pregnancy-associated plasma protein-A; MoM: Multiples of the median; βhCG: Beta-human chorionic gonadotropin.

Table 2: Evaluations according to groups

	Control (n=30)	Plasenta previa without PAS (n=37)	Placenta previa with PAS (n=30)	p
Age (years), Mean±SD	30.57±2.57	32.86±4.29	33.30±4.76	[3]0.020*
Body mass index (k/m^2), Mean±SD	25.34±3.95	25.76±4.21	27.75±5.08	[3]0.106
PAPP-A (MoM), Mean±SD (Median)	1.04±0.46 (1.01)	1.29±1.13 (0.99)	1.16±0.70 (0.99)	[4]0.963
βhCG (MoM), Mean±SD (Median)	0.96±0.43 (0.86)	1.08±0.72 (0.84)	1.27±0.79 (1.06)	[4]0.379
Birth weight (gram), Mean±SD	3174.3±420.6	2680.2±709.6	2434.8±703.3	[3]0.001**
Gestational week at delivery Mean±SD	38.20±1.27	35.41±3.42	33.62±3.26	[3]0.001**
Ceserean history, n (%)				[5]0.001**
0	8 (26.7)	25 (67.6)	6 (20)	
1	18 (60)	12 (32.4)	8 (26.7)	
≥2	4 (13.3)	0 (0)	16 (53.3)	
Blood transfusion, n (%)				[5]0.001**
–	30 (100)	31 (83.8)	4 (13.8)	
+	0 (0)	6 (16.2)	25 (86.2)	

3: Oneway ANOVA Test; 4: Kruskall Wallis H Test; 5: Ki-Kare Test; *: P<0.05; **: P<0.01; n: Number; PAPP-A: Pregnancy-associated plasma protein-A; MoM: Multiples of the median; βhCG: Beta-human chorionic gonadotropin.

in the previa group (p<0.01) (Table 1). The gestational age at birth was statistically significantly higher in the control group than in the previa group (p<0.01) (Table 1). A statistically significant difference in the rates of blood transfusion was determined between the groups (p<0.01), with the rate of blood transfusion significantly higher in the previa group than in the control group (Table 1).

A statistically significant difference was also detected in the mean ages between the groups (p<0.05). Pairwise comparisons to determine the source of this difference revealed that the mean age was significantly higher in the PAS group than in the control group (p<0.05). No significant difference was noted in the mean ages between the placenta previa without PAS group and control group (p>0.05) (Table 2).

Table 3: Evaluations according to groups

	Control (n=30)	With hysterectomy (n=53)	Without hysterectomy (n=14)	p
Age (years), Mean±SD	30.57±2.57	33.11±4.12	32.86±5.81	[3]0.021*
Body mass index (k/m^2), Mean±SD	25.34±3.95	26.37±4.58	27.69±5.16	[3]0.300
PAPP-A (MoM), Mean±SD (Median)	1.04±0.46 (1.01)	1.24±1.01 (0.99)	1.21±0.78 (1.04)	[4]0.951
βhCG (MoM), Mean±SD (Median)	0.96±0.43 (0.86)	1.07±0.66 (0.84)	1.52±0.99 (1.45)	[4]0.249
Birth weight (gram), Mean±SD	3174.33±420.63	2603.98±769.92	2455.0±436.63	[3]0.001**
Gestational week at delivery, Mean±SD	38.20±1.27	34.92±3.73	33.50±1.65	[3]0.001**
Ceserean history, n (%)				[5]0.001**
0	8 (26.7)	30 (56.6)	1 (7.1)	
1	18 (60)	17 (32.1)	3 (21.4)	
≥2	4 (13.3)	6 (11.3)	10 (71.4)	
Blood transfusion, n (%)				[5]0.001**
–	30 (100)	34 (65.4)	1 (7.1)	
+	0 (0)	18 (52)	13 (92.9)	

3: Oneway ANOVA Test; 4: Kruskall Wallis H Test; 5: Ki-Kare Test; *: P<0.05; **: P<0.01; n: Number; With Hysterectomy:Hysterectomy (+); With Hysterectomy:Hysterectomy (-); PAPP-A: Pregnancy-associated plasma protein-A; MoM: Multiples of the median; βhCG: Beta-human chorionic gonadotropin.

A statistically significant difference was found in birth weights between the groups (p<0.01). Pairwise comparisons to determine the source of the difference revealed that the mean birth weight was significantly higher in the control group than in either the placenta previa without PAS group or the PAS group (Table 2).

A statistically significant difference was determined in the gestational ages at birth between the groups (p<0.01). Pairwise comparisons to determine the source of the difference showed that the mean gestational age at birth was significantly higher in the control group than in either the placenta previa without PAS group or the PAS group. The gestational age at birth was also significantly higher in the placenta previa without PAS group than in the PAS group (Table 2).

A statistically significant difference was observed in the history of C/S between the groups (p<0.01). The number of C/S cases was significantly higher in the PAS group than in either the control group or the placenta previa without PAS group (Table 2).

A statistically significant difference was detected in the rates of blood transfusion between the groups (p<0.01). The rate of blood transfusion was significantly higher in the PAS group than in either the control or the placenta previa without PAS group (Table 2).

The mean birth weight of the control group was significantly higher than both the Hysterectomy (-) and Hysterectomy (+) groups. Additionally, the mean gestational age of the control group was significantly higher than both the Hysterectomy (-) and Hysterectomy (+) groups. The C-section rate in the Hysterectomy (+) group was significantly higher than both the control group and the Hysterectomy (-) group (Table 3).

DISCUSSION

Disorders within the placenta accreta spectrum represent a range of abnormalities in placental attachment. Subtypes of PAS include placenta accreta (creta or adherenta, PA), placenta increta (PI), and placenta percreta (PP). The incidence of PAS has undergone a dramatic increase in recent years. A study by Matsuzaki et al.[15] reported a prevalence of PAS of 0.29% among women undergoing cesarean delivery with live births in the United States. Women diagnosed with PAS face elevated risks of hemorrhage, bladder and urinary tract injuries, and the need for hysterectomy during childbirth. Early and accurate diagnosis, along with appropriate treatment planning for PAS pregnancies, is of paramount importance for preoperative multidisciplinary management and planning of PAS deliveries.

A diagnosis of PAS is preferably made through ultrasonographic evaluation, although this is operator-dependent and limited in terms of accuracy in determining the degree of posterior placental invasion and parametrial extension. In these situations, magnetic resonance imaging (MRI) is helpful, but MRI is not recommended as a routine diagnostic approach due to its high cost and limited clinical value.[16] Thus, the true performance of MRI remains to be confirmed by independent studies.[17]

At present, radiological strategies, such as ultrasound technology, remain the primary approach for diagnosing PAS. Early prediction of PAS in pregnancy therefore relies primarily on the position of the gestational sac, but this may not provide sufficient information for a diagnosis of PAS.[18] Improving the diagnosis, assessing the severity of PAS, and predicting perioperative outcomes still require further exploration of additional diagnostic methods. In this respect, the process of detecting maternal circulation biomarkers offers an objective, non-invasive, and cost-effective method for PAS diagnosis.

Some studies have shown that biomarkers may have potential significance in the diagnosis of PAS. However, no biomarker has yet been definitively proven useful in PAS diagnosis; therefore, these biomarkers are not yet utilized in clinical practice. Nevertheless, due to the importance of early diagnosis, research on biomarkers for the early detection of PAS is continuing to increase.[16] Unlike imaging methods, which can only establish a diagnosis in advanced gestational weeks, numerous serum markers have been investigated to make earlier diagnoses.[2–4,13–18] Of these markers, PAPP-A and fβhCG are considered placental markers and have been utilized in multifactorial tests aimed at predicting placental function.[19]

Although the exact function of PAPP-A remains incompletely understood, it is known to participate in the proteolysis of insulin-like growth factor-binding protein 4 (IGFBP-4), suggesting a role for PAPP-A in placental growth. Physiologically, placental syncytiotrophoblasts secrete PAPP-A in increasing concentrations into the maternal circulation,[20] where it acts as a zinc metalloproteinase. Additionally, PAPP-A may serve as a potential marker for healthy placental trophoblasts,[21] as it is overexpressed in the first trimester and may be involved in trophoblast invasion that could lead to the pathogenesis of PAS.[22]

A recent meta-analysis assessed eight research studies (seven retrospective and one prospective) involving 243 PAS patients and 1599 non-PAS pregnant women. The age range was between 32 and 35 years, and the MoM values were compared. Five studies reported an association between PAPP-A and PAS, while three studies found no clear association. The limitations of the meta-analysis included the small number of patients, the reliance on mostly retrospective studies and, most importantly, the inability to confirm a causal relationship between high PAPP-A levels and the development of PAS during pregnancy. Based on the meta-analysis results, the authors concluded that further studies are needed to investigate the optimal cut-off points for serum PAPP-A levels in the first trimester when attempting to use PAPP-A as a predictor of PAS.[7] In our study, neither the BMI nor the PAPP-A or free βhCG measurements showed statistically significant differences between any of the groups ($p>0.05$).

Serum levels of free beta hCG (fβhCG) have also been proposed as another PAS indicator in the first trimester. The screening test probes for the beta subunit of the glycoprotein hormone hCG. While predominantly produced by syncytiotrophoblasts, this hormone is also synthesized by fetal kidney and liver tissues. Thus, the concentrations of fβhCG gradually increase during early pregnancy, peaking between the 8th and 10th weeks of gestation. Besides sustaining the function of the corpus luteum, fβhCG also plays a role in promoting angiogenesis, cytotrophoblast differentiation, immunosuppression, and inhibiting the phagocytosis of invading trophoblast cells.[23,24]

Several studies in the literature have assessed βhCG levels. For example, Desai et al.[13] did not observe a significant difference in first-trimester βhCG levels in their PAS group. By contrast, two other studies indicated increases in βhCG MoM values of up to 1.5 times in cases of accreta.[14,25] The latter authors concluded that βhCG MoM values still exhibit differences and require further evaluation through advanced research.[13] In the present study, our results indicated no significant differences in the βhCG MoM values in our groups.

The disadvantage of using biomarkers, such as PAPP-A and βhCG, for the diagnosis of PAS is that these biomarkers are often not specific to PAS and are also associated with other comorbidities and adverse complications that can arise during pregnancy.[26,27] In addition, PAPP-A levels are influenced by ethnic origin and BMI.[7,13,14,28,29] In our study, the pregnant women selected for the control group had similar ethnic backgrounds and their BMI averages were also within similar ranges, but we assumed that our study results were not influenced by these variables. Another finding in the literature is that PAS patients tend to be older. In our study, the average age of our patients was significantly higher in the PAS group than in the control group.

CONCLUSION

Whether PAPP-A and βhCG are involved in the pathogenesis of PAS remains unclear. Investigating these markers in combination with ultrasound and MRI may provide more useful information. Further prospective research is needed to evaluate these aspects of PAS.

Statement

Ethics Committee Approval: The Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 23.06.2021, number: 134).

Author Contributions: Concept – ÇYA; Design – ÇYA; Supervision – ÇK, ÇYA; Resource – BD; Materials – RK; Data Collection and/or Processing – AÖ, ÇK, RK, İÇ; Analysis and/or Interpretation – BD, ÇK; Literature Search – ÖS, RK; Writing – ÇYA, ÖS; Critical Reviews – ÇYA, RK, ÖS.

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