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First Trimester Screening of High-Risk Cases for Placenta Accreta by Using Transvaginal Scan and Serum PAPP-A: A Preliminary Study

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ABSTRACT

Background: Placenta accreta spectrum (PAS) presents substantial risks to maternal and fetal well-being, emphasizing the need for early detection and intervention strategies. **Objective:** This study aimed to evaluate the efficacy of first-trimester ultrasound screenings and pregnancy-associated plasma protein A (PAPP-A) testing in detecting PAS.

Methods: This prospective study analyzed data of 88 patients who underwent first-trimester ultrasound screening and PAPP-A testing to evaluate the accuracy of early diagnostic methods for placenta accreta spectrum (PAS).

Results: 88 patients with mean age of 30.75 years and BMI of 26.92 kg/m^2 were included in this study. 38.6% had ≥ 3 prior CS. Patients with placenta accreta (n=13) had significantly higher BMI (32.7 vs. 26.0, p<0.001) and prior CS (3.2 vs. 2.3, p<0.001). First-trimester ultrasound had 92.3% sensitivity and 98% NPV, while PAPP-A alone was of weak predictive value (AUC = 0.546, p=0.597).

Conclusion: First-trimester PAPP-A was not a good predictor for diagnosing placenta accreta spectrum (PAS) but may have added value. Transvaginal ultrasound remains the preferred modality and is more reliable for screening early, particularly in high-risk populations. Combined marker strategies need to be developed to improve early detection and maternal outcomes.

Keywords: Placenta accreta spectrum, First-trimester ultrasound, PAPP-A testing, Prenatal care, Maternal-fetal outcomes.

INTRODUCTION

Placenta accreta, characterized by abnormal adherence of the placenta to the uterine wall, poses significant risks during pregnancy and childbirth. It encompasses placenta accreta, increta, and percreta, with accreta being the most common form, accounting for approximately 75% of cases. These conditions often lead to incomplete separation of the placenta post-delivery, resulting in severe postpartum hemorrhage, a leading cause of maternal mortality [1, 2].

Risk factors for placenta accreta include multiparity, advanced maternal age, placenta previa, prior uterine surgery, and previous Cesarean section. The incidence of placenta accreta has risen globally, particularly in tandem with rising rates of Cesarean sections, reaching rates of 1 in 2510 to 1 in 533 pregnancies, with even higher rates noted in developing countries [3, 4].

Placenta accreta presents a substantial clinical burden, accounting for a significant proportion of emergency peripartum hysterectomies. Early screening and diagnosis are crucial for mitigating risks associated with placenta accreta, improving maternal outcomes, and optimizing presurgical planning. Sonography with grayscale and color Doppler imaging is the preferred modality for diagnosing morbidly adherent placenta, with various ultrasound markers indicating its presence [5, 6]. While placenta accreta is typically diagnosed in the second or third trimester, there is growing evidence suggesting that sonographic findings suspicious for placenta accreta may be detectable as early as the first trimester. Pregnancy-associated plasma protein A (PAPP-A), a glycoprotein secreted by syncytial trophoblasts and decidua, is a marker measured in the first trimester and is indicative of certain pregnancy complications, including placenta accreta [7].

This study aimed to investigate whether PAPP-A levels in the first trimester differ among pregnancies with placenta accreta and whether combining first-trimester ultrasound with PAPP-A measurement improves the early prediction of placenta accreta.

PATIENTS AND METHODS

This prospective study included 88 pregnant women and was conducted at The Fetal Medicine Unit of Al Kasr Al-Aini Hospitals from June 2016 to December 2018. The study aimed to investigate the predictive value of (PAPP-A) in the first trimester for placenta accreta among pregnant women between 11 to 14 weeks of gestational age, confirmed by either the last menstrual period (LMP) or crown-rump length (CRL).

Inclusion criteria: History of previous lower segment cesarean section (LSCS), previous myomectomy, or hysteroscopic removal of septum or myoma.

Exclusion criteria: Multiple pregnancies, previous uterine scar with fundal implantation of the sac, and congenital uterine malformations such as bicornuate or septate uterus.

Procedures: Blood samples for PAPP-A measurement were collected from all participants in the first trimester. The samples were processed by centrifugation, and the serum was collected for PAPP-A assay using electro-chemiluminescent technique and PAPP-A ELISA Kit.

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The kit employed a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of human pregnancy-associated plasma protein A (PAPP-A) in the samples.

The ultrasound screening procedure for placenta accreta was performed using transvaginal (TV) ultrasound in the first trimester, utilizing a high-resolution ultrasound machine equipped with a 5–9 MHz transvaginal probe. This approach provided enhanced visualization of the lower uterine segment and uterine scar, particularly in patients with a history of lower segment Cesarean section (LSCS) or other uterine surgeries. The screening focused on detecting key ultrasound markers including identification of the uterine scar, trophoblast and placental location, loss of the retroplacental clear zone, measurement of the smallest myometrial thickness, irregularity of the uterine-bladder interface, presence of placental lacunae, and bridging vessels.

Follow-up assessments were conducted with a second visit between 28 to 36 weeks to identify abnormal placenta. Intraoperative diagnostic criteria for abnormal invasive placenta during Cesarean section were defined. Participants were followed up for obstetric outcomes, including term delivery, preterm delivery, abortion, or Cesarean scar pregnancy (CSP).

Ethical approval: Ethical approval was obtained from The IRB committee of Faculty of Medicine, Menoufia University, in alignment with the principles of the Declaration of Helsinki and local regulations. Prior to the commencement of any study-related procedures, informed consent was obtained from each participant, involving a comprehensive explanation of the study's objectives, potential risks, and benefits.

Statistical Analysis

Data collected were tabulated and statistically analyzed using IBM SPSS Statistics version 26. For descriptive statistics and analytic statistics, Student's t-test, Mann-Whitney's test, Chi-square test, and Receiver Operating Characteristic (ROC) curves, were performed to evaluate the predictive value of PAPP-A in the first trimester for placenta accreta. $P \leq 0.05$ was deemed significant.

RESULTS

Table (1) provided the baseline features of the 88 studied patients. The mean maternal age was 30.75 years and mean BMI was 26.92 kg/m^2. Most of the patients presented with a median parity of 3 and gravida of 4. A history of prior Cesarean deliveries was common, with nearly 38.6% having undergone three previous CS. The mean gestational age at first-trimester ultrasonography was 12.14 weeks and the median PAPP-A MoM was 1. Antepartum hemorrhage was present in 4.5% of cases.

Table (1): characteristics of studied patients regarding demographic and clinical characters:

Variable		Studied cases No.=88
Age (years): (Mean ±SD)		30.75±5.5
BMI (Mean ± SD)		26.92±5.
Gravida	Range	1 – 10
	Median (IQR)	4 (3 – 5)
Parity	Range	0-6
	Median (IQR)	3 (2 – 3)
Prior CS No. (%)		
One		12(13.6%)
Two		32(36.4%)
Three		34(38.6%)
Four		6(6.8%)
myomectomy		4(4.5%)
Gestational age by TVUS (Mean ± SD)		12.14±1.18
PAPP-A		
Median of MOM		1
Range		0.13 – 11.92
APH No. (%)		4(4.5%)

Table (2) showed that patients who presented with placenta accreta had a significantly higher BMI ($p<0.001$), parity ($p=0.009$), and number of previous Cesarean sections ($p<0.001$) than those who did not present with accreta. The maternal age, gravida, or PAPP-A MoM levels were not significantly different between the groups.

Table (2): Comparison between patients with placenta accrete and non-accrete regarding demographic and clinical characters:

Variable	Placentae accrete group N = 13	Non-Placenta accrete group N = 75	P value
Age (years): (Mean ±SD) Range	32.85±3.96 28-42	30.42±5.8 18-41	0.138
BMI (Mean ± SD) Range	32.69±4.64 25-38	25.96±4.7 17-39	<0.001**
Gravida Median (IQR)	4 4-5	4 3-5	0.059
Parity (Mean ±SD) Range	3.38±0.77 2-5	2.61±1.05 1-6	0.009*
Prior CS (Mean ±SD) Range	3.23±0.59 2-4	2.25±0.77 1- 4	<0.001**
PAPP-A Median of MOM (range)	0.93 0.25 – 1.69	1 0.13 - 11.92	0.597

Table (3): illustrated the ultrasound markers over trimesters. Placental position was consistent, with anterior placenta in most cases. Significantly, loss of clear zone and irregular placental lacunae was more frequent in the first trimester, while vascular lacunae and bridging vessels showed little fall or stability with time.

Table (3): Ultrasound finding in first (11-14 weeks) and second trimester (28-36 weeks):

Variable	First trimester		Second trimester	
	N	%	N	%
Placental location				
Anterior	67	76.1	66	75
Posterior	18	20.5	19	21.6
Anterior covering IO	2	2.3	2	2.3
posterior covering IO	1	1.1	1	1.1
Loss of clear zone	32	36.4	23	26.1
Abnormal placental lacunae	39	44.3	45	51.1
Vascular placental lacunae	31	35.2	17	19.3
Bridging vessels	20	22.7	17	19.3

This study confirmed the limited diagnostic utility of PAPP-A MoM as a sole predictor for placenta accreta with an area under curve (AUC) of 0.546. Although sensitivity was relatively high (79.9%), specificity was low (40%), and the result was not statistically significant (p=0.597) (Table 4 & figure 1).

Table (4): ROC curve analysis of the optimal cutoff of MOM of PAPP-A in prediction of placenta accreta

	Cutoff point	AUC	Sensitivity%	Specificity%	P value	95%CI Lower - Upper
	≤0.89	0.546	79.9%	40%	0.597	0.304 – 0.603

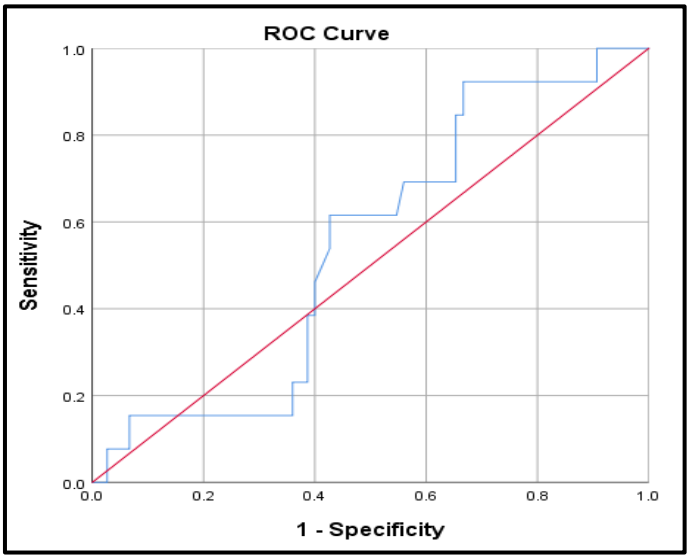

Figure (1): Receiver operating characteristic curve (ROC) analysis of the optimal cutoff of MOM of PAPP-A in prediction of placenta accrete.

Table (5) contrasted the diagnostic performance of first-trimester ultrasound alone with that for first-trimester ultrasound and PAPP-A. First-trimester ultrasound alone had excellent sensitivity (92.3%) and negative predictive value (98%), an indicator of its usefulness in ruling out placenta accreta. The combination with PAPP-A did not increase diagnostic performance and decreased specificity and predictivity.

Table (5): Overall screening parameter of first trimester ultrasound for diagnosis of placenta accreta

	Sensitivity	Specificity	Predictive value of +ve result	Predictive value of -ve result	Accuracy
Ultrasound	92.3%	61.3%	29%	98%	66%
PAPP-A in combination with the ultrasound	92.3%	41.3%	21.4%	96.8%	50.6%

DISCUSSION

Placenta accreta is a serious obstetric complication characterized by abnormal placental implantation, which can result in life-threatening bleeding, shock, uterine perforation, and even maternal death. Its incidence has markedly increased in recent decades, and early diagnosis is crucial to reduce peripartum complications [8].

While ultrasound and MRI are commonly used for prenatal detection, their accessibility and diagnostic accuracy remain limited, highlighting the need for more sensitive and widely available tools. Serum analytes, particularly those assessed in the first trimester, may aid in early risk stratification. Among them, PAPP-A, known for its role in placental development and its association with adverse outcomes such as pre-eclampsia and preterm birth, may be relevant. Placenta accreta involves excessive trophoblast invasion and decidual deficiency, in contrast to the shallow invasion seen in pre-eclampsia [9, 10]. Given the unclear relationship between PAPP-A levels and placenta accreta, the aim of our study was to evaluate the efficacy of first-trimester ultrasound screenings and PAPP-A testing in detecting PAS.

In this study of 88 pregnant women undergoing first-trimester screening, the baseline characteristics revealed the mean maternal age was 30.75 years and the mean BMI was 26.92kg/m^2, with most of the women having a median gravida of 4 and parity of 3. A significant proportion (38.6%) had three previous Cesarean sections, indicating the high-risk nature of the cohort. These findings are aligned with **Wu *et al.*** [11] and **Dayem** [12] who also noted prior uterine surgery and Cesarean section as significant risk factors for placenta accreta spectrum (PAS). **Ma *et al.*** [13] also noted similar demographics of mothers, including age, BMI, and parity, among women with risk factors for PAS.

While our study reported a relatively low incidence of antepartum hemorrhage (4.5%), **Wang *et al.*** [8] noted a higher incidence of vaginal bleeding in the placenta previa–accreta subgroup, indicating the clinical significance of abnormal placentation.

When patients with and without placenta accreta were compared, our results showed that significantly higher BMI, parity, and previous Cesarean sections were observed in the accreta group. That the maternal age, gravida, or first-trimester PAPP-A levels did not differ significantly between the two groups was observed. These findings partly vary from several reports in the literature regarding the predictive value of PAPP-A. **Wang *et al.*** [8] **and Desai *et al.*** [14] also supported the association of elevated PAPP-A levels with PAS, wherein elevated PAPP-A in early pregnancy can serve as a valuable marker for invasive placentation. Similarly, **Balkaş & Caglar** [10] observed significantly higher median values of PAPP-A in cases of PAS (1.96) compared to non-adherent placenta previa (0.88) and healthy controls (0.89), with high statistical significance ($p<0.001$). These studies intimate that elevated PAPP-A levels can be a reflection of increased trophoblastic invasion and can be an indicator of abnormally adherent placenta. In contrast, our findings have greater concordance with the observations of **Wu *et al.*** [11] and **Dayem** [12], who both reported significantly lower levels of PAPP-A in patients with PAS. These authors proposed that defective trophoblastic invasion or defective placental development, rather than hyperinvasive implantation, may account for observed PAS pathology in some cases, particularly when it occurs with scarring from previous Cesarean sections. **Ma *et al.*** [13] also described differences in serum markers, both PAPP-A and β-hCG, between PAS and non-PAS groups, suggesting that marker patterns may vary based on clinical circumstance and the pathogenetic mechanism of accreta development.

In light of these conflicting results, the utility of PAPP-A alone as a stable marker for early PAS diagnosis is uncertain. While some studies provide support for its utilization in early screening programs, others have challenged its predictive ability as limited or heterogeneous. As it stands, the integration of maternal risk factors, detailed ultrasound assessment, and perhaps biomarker panels will present a more robust approach to early PAS detection.

ROC curve analysis in the current study revealed that first-trimester PAPP-A MoM possessed limited predictive value with an AUC curve of only 0.546. While the test was demonstrated to have relatively high sensitivity (79.9%), it lacked specificity (40%), and correlation was statistically non-significant ($p=0.597$). Thus, PAPP-A alone would not be a useful single predictor for placenta accreta.

This finding is in contrast to several earlier works favoring increased potential for the function of PAPP-A. For instance, **Balkaş & Caglar** [10] and **Desai *et al.*** [14] both identified considerably higher PAPP-A MoM in PAS patients and suggested its application in preliminary screening tests. Similarly, **Wang *et al.*** [8] hypothesized altered first-trimester markers like PAPP-A could be beneficial in detecting pregnancies at risk of complications involving the placenta.

On the other hand, our findings are in agreement with **Wu *et al.*** [11]**, Dayem** [12] and **Ma *et al.*** [13] who all reported reduced PAPP-A MoM values in PAS cases and questioned its application as a single screening test. **Wu *et al.*** [11] proposed a cut-off level of < 0.45 MoM, while **Dayem** [12] proposed < 0.5 MoM, both of which had moderate sensitivity and specificity. In addition, **Schiffer *et al.*** [15] correlated low PAPP-A with maternal vascular malperfusion (MVM), a placental condition frequently seen in tandem with PAS. Therefore, the conflicting results between studies highlight the pathophysiological heterogeneity of PAS and the need to interpret serum marker levels in the context of clinical risk factor and imaging findings.

Diagnostic accuracy of first-trimester ultrasound with and without PAPP-A showed that first-trimester ultrasound in our study had good sensitivity (92.3%)

and high negative predictive value (98%), and therefore was effective at ruling out PAS. Unfortunately, as hoped, incorporating PAPP-A into ultrasound assessment did not enhance diagnostic accuracy. In fact, it reduced specificity and dampened overall predictive performance. This result is partly contrary to certain studies favoring integrated models. For example, **Wu *et al.* [11], Dayem [12]** and **Desai *et al.* [14]** all suggested that the application of ultrasound with serum markers such as PAPP-A increased detection rates in early stages of PAS, especially in high-risk pregnancies. **Ma *et al.* [13]** also confirmed improved diagnostic criteria when first-trimester ultrasound results were read together with maternal serum markers, primarily in placenta previa or Cesarean history.

However, our findings support **Belousova *et al.* [16]** in highlighting that although ultrasound in isolation lacks a subset of cases of PAS, single combination with PAPP-A would not necessarily deliver consistent diagnostic benefits unless there are other markers (such as β-hCG) added. Their research confirmed that PAPP-A and free β-hCG combination provided superior performance compared to ultrasound, which suggests that multi-marker panels are superior to the use of PAPP-A in isolation.

CONCLUSION

This research emphasized that first-trimester PAPP-A levels alone offered limited accuracy in predicting placenta accreta spectrum (PAS), though they may serve as an additional indicator. Transvaginal ultrasound continues to be the most dependable method for early identification, particularly in women at elevated risk. Ongoing efforts to refine and integrate multiple diagnostic markers are essential to advance early recognition and enhance maternal health outcomes. Standardized screening protocols and further research are essential to optimize PAS detection and management, enhancing maternal and fetal health outcomes. Prospective multicenter studies are warranted to validate the efficacy of early ultrasound screenings and inform evidence-based approaches to prenatal care.

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