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Relationship between first and second trimester aneuploidy screening test serum analytes and placenta accreta

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Abstract

Placenta accreta (PA) is a serious obstetric complication associated with maternal morbidity and mortality. While ultrasonography and MRI are effective in the third trimester, early diagnosis in the first two trimesters remains elusive. This study aims to explore the utility of biochemical markers in early PA detection, addressing a critical gap in current diagnostic approaches. A retrospective analysis was conducted on patients diagnosed with placenta previa between October 2021 and December 2022. Cases were divided into PA and non-PA groups based on histopathological examination. Demographic, obstetric characteristics and serum analytes were compared between the groups to identify potential biomarkers for early PA detection. Patients with PA exhibited higher gravida, parity, and abortion numbers. First-trimester free β-hCG levels and second-trimester E3 levels were significantly elevated in the PA group compared to non-accreta cases. No significant differences were observed in PAPP-A, AFP, and second-trimester hCG levels. Additionally, postoperative leukocyte count was lower, and intrapartum bleeding frequency was higher in the PA group. Multiparity and the number of previous cesarean sections emerged as significant risk factors for PA, consistent with previous literature. While previous studies reported associations between biochemical markers and PA, this study uniquely identified significant associations with free β-hCG and E3 levels. Further research is warranted to validate these findings and elucidate their clinical implications.

Keywords: AFP, E3, free β-hCG, hCG, PAPP-A, placenta accreta

1. Introduction

Placenta accreta (PA) represents a critical obstetric concern associated with maternal morbidity and mortality. Despite advancements in obstetric care, the early diagnosis of PA remains challenging, particularly during the first two trimesters of pregnancy. This diagnostic difficulty stems from the lack of definitive methods to detect PA in its early stages, necessitating exploration into alternative diagnostic approaches (1).

PA incidence has been on the rise, attributed to factors such as advanced maternal age, in vitro fertilization, and previous uterine surgeries, notably cesarean sections (2). The risk of PA escalates with repeated cesarean sections, with a pronounced 61% risk observed after three procedures (3). PA poses a significant threat to maternal health, accounting for a substantial portion of major hemorrhages and peripartum hysterectomies, and contributing to approximately 7% of maternal deaths during pregnancy (4). Its impact extends beyond hemorrhage, increasing the risk of disseminated intravascular coagulation and organ injury (5).

Current diagnostic modalities, such as ultrasound and MRI, demonstrate high efficacy in the third trimester but lack definitive diagnostic utility in earlier stages of pregnancy (6). Consequently, there is a pressing need for novel diagnostic tools to enable early identification of PA. Biochemical markers have emerged as promising candidates for early PA detection, as they reflect underlying placental pathology associated with trophoblastic invasion (7).

Previous studies have highlighted associations between biochemical markers and placental invasion. Notably, Pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonadotropin (free β-hCG), markers utilized in first-trimester anomaly screening, have shown potential relevance to PA (8). Additionally, markers such as alpha-fetoprotein (MS-AFP), human chorionic gonadotropin (hCG), and Estriol (E3) used in second-trimester screening tests have also been implicated in PA pathology (9).

In this study, we aim to leverage the diagnostic potential of first and second-trimester biochemical parameters, traditionally employed in Down syndrome screening, for early PA detection. By examining the associations between these markers and PA, we seek to contribute to the development of effective diagnostic strategies for this life-threatening obstetric complication.

2. Materials and methods

A retrospective analysis was conducted using patient records

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from Mersin City Training and Research Hospital, covering the period from October 2021 to December 2022. The study focused on individuals diagnosed with placenta previa, excluding those with high (>1/300) first and second-trimester screening test results, as well as patients with hypertension, diabetes, thyroid disorders, or multiple pregnancies. Diagnosis of placenta accreta was confirmed through histopathological examination of hysterectomy or local excision specimens.

Patients with placenta previa were categorized into two groups: accreta and non-accreta, based on histopathological findings. The accreta group comprised 27 patients, while the non-accreta group included 68 patients.

During the first trimester scans, conducted between 11 weeks and 13 weeks + 6 days, maternal serum levels of free β-hCG and PAPP-A were measured using automatic devices. Second-trimester scans, performed between 16 weeks and 19 weeks + 6 days, included measurements of biparietal diameter (BPD) and maternal serum levels of hCG, E3, and AFP. MoM values for these markers were adjusted according to gestational week. Additionally, obstetric histories, demographic characteristics, and complete blood count parameters were documented. Statistical analysis was conducted using SPSS software (IBM SPSS statistical version 24.0, Armonk, NY, USA). Normality distribution of variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, while the homogeneity of variances was examined using the Levene test. Mean and standard deviation (SD) were calculated for normally distributed variables, whereas median, minimum, and maximum values were determined for non-normally distributed variables. Differences between mean values were evaluated using Student's t-test or Mann-Whitney U test, while the Chi-square test was applied for categorical variables. A p-value of <0.05 at the 95% confidence interval was considered statistically significant.

3. Results

Ninety-five patients diagnosed with placenta previa were enrolled in the study, of whom 27 were identified to have Placenta Accreta (PA) based on histopathological examination. In comparison, the remaining 68 patients showed no signs of placental invasion.

Comparative analysis revealed no significant differences between the two groups regarding age, week of birth, and fetal birth weight. However, the PA group exhibited significantly higher gravidity, parity, and abortion counts compared to the non-PA group (p<0.001 for all).

First-trimester serum levels of free β-hCG were found to be significantly elevated in the PA group compared to the non-PA group (p=0.02), whereas no significant differences were observed in PAPP-A levels between the groups (p=0.20).

In terms of second-trimester screening, maternal serum E3 levels were significantly higher in the PA group compared to the non-PA group (p=0.03). However, no statistically significant differences were noted in AFP and hCG levels between the two groups.

Preoperative hemoglobin levels were significantly higher in the placenta accreta group (p=0.04), whereas postoperative leukocyte levels were significantly lower (p=0.001). No significant differences were observed in other complete blood count parameters. (Table 1)

Table 1. Demographic characteristics and mean blood parameters of the groups

	PA present Mean±SD	PA absent Mean±SD	p
Maternal age (year)	34±7	35±6	0.42
Gestational age (week)	37±2.5	37±2.1	0.39
Fetal birth weight (Gr)	2956±606	2823±753	0.45
Gravida	**2.6±1.6**	**1.0±0.5**	***<0.001***
Parita	**1.2±1.1**	**0.5±0.4**	***<0.001***
Abortus	**0.5±0.7**	**0.0±0.5**	***<0.001***
PAPP-A (MoM)	1.42±0.77	1.18±0.55	0.20
free β-hCG (MoM)	**1.76±1.08**	**1.21±0.49**	***0.02***
Estriol (E3) (MoM)	**0.87±0.16**	**0.84±0.36**	***0.03***
hCG (MoM)	2.23±0.84	1.31±0.94	0.92
AFP (MoM)	1.52±1.05	0.95±0.66	0.56
Preoperative hemoglobin (g/dL)	**11.8±1.32**	**11.5±0.9**	***0.04***
Preoperative hematocrit (%)	35.1±3.6	34.1±2.4	0.09
Preoperative white blood cell count (M/µL)	11.1±4.45	10.1±2.7	0.29
Preoperative platelet count (K/µL)	210±65	219±58	0.52
Postoperative hemoglobin (g/dL)	10.0±1.33	10.1±1.36	0.89
Postoperative hematocrit (%)	29.8±3.7	29.8±3.8	0.57
Postoperative white blood cell count (M/µL)	**13.3±3.3**	**14.5±5.0**	***0.01***
Postoperative platelet count (g/dL)	179±57	187±54	0.35

Furthermore, the incidence of PA was found to increase proportionally with the number of cesarean sections, particularly among those with three or more previous cesarean deliveries (p<0.001). The PA group also demonstrated a significantly higher occurrence of intrapartum bleeding and interventions to manage bleeding, including uterine artery ligation, Bakri balloon application, uterine artery ligation combined with Bakri application, and hypogastric artery ligation (p<0.001). However, there were no significant differences between the groups regarding the number of intrapartum hysterectomies. (Table 2).

Table 2. Number of previous cesarean sections and intrapartum complication rates

	PA present N (%)	PA absent N (%)	Total	P
First cesarean section	11	64	75	
Second cesarean section	4	4	8	***<0.001***
3 and more cesarean section	12	0	12	
No complications	7	60	67	
Uterine artery ligation	8	0	8	
Bakri balloon application	4	5	9	
Uterine artery ligation and Bakri balloon	3	1	4	
Hypogastric artery ligation	4	0	4	***<0.001***
Hypogastric artery ligation and Bakri balloon	0	1	1	
Hysterectomy	1	1	2	
Total	27	68		

4. Discussion

Placenta accreta (PA) stands as a formidable obstetric complication, posing significant risks to maternal and fetal health (10). Our study endeavors to contribute to the advancement of early diagnostic strategies for PA, recognizing the urgent need for interventions to mitigate associated morbidity and mortality.

In concordance with existing literature, our findings underscore the pivotal role of certain demographic factors in predisposing individuals to PA. Notably, multiparity and a history of multiple cesarean deliveries emerged as significant risk factors, aligning with prior studies that have highlighted their association with placental abnormalities (11, 12) This emphasizes the importance of comprehensive obstetric history assessments in identifying pregnancies at heightened risk of PA, particularly in the context of escalating cesarean section rates worldwide (13).

Moreover, our analysis sheds light on potential biochemical markers that may hold promise for early detection of PA. Elevated levels of free β-hCG, consistent with previous research, emerged as a promising indicator of placental invasion anomalies (14, 15). However, the lack of significant correlation between Pregnancy-associated plasma protein A (PAPP-A) levels and PA in our study diverges from some existing literature, suggesting the need for further exploration into its diagnostic efficacy (16, 17).

While second-trimester markers such as human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) did not exhibit significant differences between PA and non-PA groups in our study, the unexpected elevation of Estriol (E3) levels in the PA group warrants careful consideration (18, 19). This unexpected finding challenges previous assumptions and underscores the complexity of PA pathophysiology, urging further investigation into its underlying mechanisms.

Our study suggests that certain parameters from both first and second-trimester screening tests, particularly free β-hCG and Estriol, hold promise for early PA diagnosis. However, comprehensive validation through larger-scale, multicenter studies is imperative to establish standardized diagnostic approaches and improve outcomes for pregnancies affected by PA. Additionally, exploring the interplay between maternal characteristics, biochemical markers, and placental pathology could provide further insights into the mechanisms underlying PA development and inform targeted preventive strategies.

While this study offers valuable insights into the early detection of placenta accreta using biochemical markers, several limitations should be acknowledged. Its retrospective nature introduces biases and potential data incompleteness. Conducted at a single center, the findings may lack generalizability, compounded by the relatively small sample size, particularly of patients with placenta accreta. Focusing solely on placenta previa patients might not fully capture the broader population at risk. Additionally, while biochemical markers show promise, they may not suffice as standalone diagnostic tools and necessitate validation through larger prospective studies. Despite these limitations, the study presents significant strengths. It addresses a crucial gap in the literature by exploring early diagnostic strategies for placenta accreta, employing a robust study design with histopathological confirmation. The inclusion of both first and second-trimester serum analytes provides a comprehensive assessment, while meticulous statistical analysis enhances credibility. Moreover, the study's critical evaluation of findings in the context of existing literature underscores its contribution to advancing knowledge in obstetric care.

Ethical Statement

Ethical approval was granted by the Clinical Research and Publication Ethics Committee of Toros University (26.12.2022, No: /195).

Conflict of interest

Authors declare that there is no conflict of interest for this article.

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Authors' contributions

Concept: C.T., S.K., T.K., Design: C.T., S.K., T.K., Data Collection or Processing: C.T., S.K., T.K., Analysis or

Interpretation: C.T., S.K., T.K., Literature Search: C.T., S.K., T.K., Writing: C.T., S.K., T.K.

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