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Complete blood count parameters in the antepartum diagnosis of placental invasion anomalies

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Abstract

Aim: Complete blood count (CBC) parameters are used to assess subclinical inflammation in various malignancies and autoimmune diseases. The abnormal trophoblastic invasion in placenta previa, similar to uncontrolled tumor cell growth, occurs with acute and chronic inflammation. Accordingly, this study aimed to evaluate the clinical utility of CBC parameters for the antepartum diagnosis of placental invasion anomalies.

Materials and Methods: The study was designed as a retrospective case-control study and carried out at our tertiary obstetric clinic between January 2016 and December 2019. A total of 181 participants were divided into three groups as follows: 77 patients who underwent a cesarean section with a diagnosis of Placenta previa (PP), 52 patients with a histopathologically confirmed diagnosis of Placenta Accreata Spectrum (PAS), and 52 control patients without PAS and without PP. Complete blood count (CBC) parameters were evaluated and compared.

Results: White blood cell ($p<0.001$), neutrophil count ($p=0.005$) and neutrophil-to-lymphocyte ratio ($p=0.002$) were found to be significantly higher, mean platelet volume ($p<0.001$) and plateletcrit levels ($p=0.050$) were significantly lower in the Placenta Previa group compared to the control group. Also, neutrophil-to-lymphocyte ratio ($p<0.001$) and platelet distribution width ($p=0.027$) were higher, and lymphocyte count ($p=0.021$), mean platelet volume ($p<0.001$) and plateletcrit ($p<0.001$) levels were lower in Placenta Accreta Spectrum group compared to the control group. In multivariate analyses, mean platelet volume (OR 4.01; 95% CI 2.4–6.6), red blood cell (OR 3.12; 95% CI 2.72–3.56) and platelet distribution width (OR 0.22; 95% CI 0.17–0.28.) were significantly associated with the placental invasion anomaly ($p<0.001$).

Discussion: Antepartum use of CBC parameters for the detection of the peripheral blood cell changes of acute and chronic inflammation secondary to placental invasion can contribute to the prediction and radiological diagnosis of placental invasion anomalies.

Keywords

Count parameters; Placenta accreta; Placental invasion; Placental migration; Placenta previa

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Introduction

Placenta previa (PP), defined as the abnormal implantation of the placenta near or over the internal cervical os, is a clinical entity with high maternal and fetal morbidity and mortality. PP is often accompanied by placental invasion anomalies, making it a leading cause of peripartum hysterectomy, as well as of third-trimester bleeding. Unlike PP, which occurs with placental implantation within the lower uterine segment, placenta accreta spectrum (PAS) is a complex disorder characterized by abnormal trophoblast invasion into the myometrium of the uterine wall, resulting from placental implantation at the defective decidualization area typically caused by preexisting damage to the endometrial-myometrial interface. It is a general term used to describe all degrees of villous invasion including accrete, increta, and percreta. The incidence of PAS disorders has risen from 0.12 to 0.31% during the last three decades [1,2]. Although the pathogenesis has not been fully elucidated, the most prominent hypothesis involves poor decidual development and/or excessive trophoblast invasion. In cases of PAS, the placental implantation area has been histopathologically shown to exhibit chronic basal inflammation with lymphoplasmacytic cell infiltration, placental vascular abnormalities with decreased maternal vascular perfusion, intraparenchymal placental hemorrhage, and decidual hemosiderosis [3,4].

In recent years, hematologic parameters and ratios from the clinically routinely used complete blood count test, including neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume, platelet count and plateletcrit, have received much attention as easily and cheaply available indicators of the systemic inflammatory state of an individual. Recent studies have demonstrated that chronic inflammation is a critical component of tumor progression, and that inflammatory cells play a key role in neoplastic processes, promoting the proliferation, survival, and migration in the tumor microenvironment. In the last several decades, it has also been shown that due to their proliferative, migratory, and invasive characteristics, decidual trophoblastic cells act similarly to cancerous cells with which they share common molecular characteristics [6]. Many studies have provided increasing evidence that the neutrophil-to-lymphocyte ratio (NLR) has a predictive and prognostic value for gynecological and urological malignancies like epithelial ovarian cancer and prostate cancer, as well as breast and colorectal cancers, which involve pathological inflammation. Similar to NLR, the platelet-to-lymphocyte ratio (PLR) has also been shown to have a prognostic value for various pathologies, including neurological (Parkinson's disease, Alzheimer's disease), autoimmune (rheumatoid arthritis, Behçet's disease, Hashimoto's thyroiditis), and cardiovascular entities [7-9].

Accordingly, given that placental/decidual trophoblasts exhibit a pseudomalignant character and an association with inflammation, this study aimed to evaluate the clinical utility of complete blood count parameters for the antepartum diagnosis of Placenta Previa without PAS and PAS.

Material and Methods

The study was designed as a retrospective case-control study and carried out at our tertiary obstetric clinic between January 2016 and December 2019. A total of 181 participants were divided into three groups as follows: 77 patients who underwent cesarean section with a diagnosis of PP (without PAS), 52 patients who had a pre- and intraoperatively established and histopathologically confirmed diagnosis of PAS, and 52 control patients without PAS and without PP. The study was approved by the Institutional Ethics Committee. Ethics board approval number is registrated date 2011-KAEK-25 2020/06-11. A written informed consent was obtained from each participant.

The PP diagnosis was made based on the presence of placental tissue lying within 20 mm of the internal cervical os or overlapping it, using transvaginal ultrasonography (US). The ultrasonographic PAS pre-diagnosis made based on a placenta invading through the myometrium and perimetrium, was postnatally confirmed histopathologically. The criteria for inclusion in the study were as follows: a history of C-section, singleton pregnancy, and gestational age ≥26 weeks (correlated by first-trimester US). Patients with systemic (endocrine, metabolic, cardiovascular, autoimmune, inflammatory) diseases, infectious and hemorrhagic complications, and a history of smoking, multiple pregnancy, and vaginal delivery were excluded. Preoperative hematologic data of the participants were obtained from the laboratory results. Obstetric characteristics (maternal age, gravidity, parity, history of miscarriage, number of previous cesarean deliveries, pregnancy length, fetal sex and weight, 1- and 5-min Apgar scores) were reviewed.

The peripheral blood samples taken from the antecubital vein for the first time preoperatively were immediately transferred into vacuum tubes containing ethylenediaminetetraacetic potassium salt and analyzed with the Beckman Coulter LH 780 Analyzer. The complete blood count parameters measured were as follows: hemoglobin (Hb), hematocrit (Hct), red blood cells (RBC), white blood cells (WBC), platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), neutrophil count (NC), and lymphocyte count (LC). The NLR and PLR were calculated.

Statistical analysis

Statistical analysis was performed using the SPSS (v. 23) software. Descriptive statistics were expressed as mean±standard deviation, number (percentage), and median (interquartile range).Conformity with normal distribution was assessed by the Kolmogorov–Smirnov test for each group and the data were generally found to be non-normally distributed. Numerical data of the three groups were compared using the Kruskal–Wallis test and the different groups were determined with post hoc stepwise step-down procedures. Intergroup differences in categorical variables were assessed with Pearson's chi-squared test. Roc analyses were used to analyse the predictive value of some variables. Multivariate regression analysis was used to show adjusted associations. The relationship between biochemical characteristics was also assessed by Spearman's rank correlation analysis for each group. A p-value less than 0.05 was considered statistically significant.

Table 1. Sociodemographic and laboratory characteristics of the study population

Variables*	Group	n	Mean	SD	Percentiles			P
					25th	Median	75th	
Age (yr)	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Gravidity	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Parity	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Abortion	Control	52	28,88	5,94	24,25	28,50	34,00	0.260
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Pregnancy length (wk)	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Birth weight (gr)	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
1-min Apgar score	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
5-min Apgar score	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Hemoglobin (gr/dl)	Control	52	28,88	5,94	24,25	28,50	34,00	0.174
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Hematocrit (%)	Control	52	28,88	5,94	24,25	28,50	34,00	0.002
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Platelet count, ×103/mm3	Control	52	28,88	5,94	24,25	28,50	34,00	0.208
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Red blood cell, ×106/mm3	Control	52	28,88	5,94	24,25	28,50	34,00	0.082
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
White blood cell, ×103/mm3	Control	52	28,88	5,94	24,25	28,50	34,00	0.002
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Neutrophil count, ×103/mm3	Control	52	28,88	5,94	24,25	28,50	34,00	0.007
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Lymphocyte count, ×103/mm3	Control	52	28,88	5,94	24,25	28,50	34,00	0.025
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Mean platelet volume (femtoliter)	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Platelet distribution width (%)	Control	52	28,88	5,94	24,25	28,50	34,00	0.039
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Plateletcrit	Control	52	28,88	5,94	24,25	28,50	34,00	0.002
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	

Neutrophil-to-lymphocyte ratio	Control	52	28,88	5,94	24,25	28,50	34,00	<0.001
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	
Platelet-to-lymphocyte ratio	Control	52	28,88	5,94	24,25	28,50	34,00	0.335
	PP	77	31,88	5,66	28,00	31,00	37,00	
	PAS	52	33,85	5,89	29,25	35,00	38,00	

*: Variables aree normall distributed, other un marked variables are not normall distributed in two groups.

Results

Sociodemographic and laboratory characteristics of the study population were demonstrated in Table 1. There was statistically significant difference between PP, PAS and control groups in terms of age, gravida, parity, gestational week at delivery, birth weight, first and fifth minutes APGAR scores, hematocrit, WBC, NC, PCT, MPV and NLR (p<o.o5 for all variable). There were statistically significant differences between the groups in terms of mean age, gravidity, and parity (p=<0.001 for each comparison). The highest and lowest mean values were observed in the PAS and control groups, respectively. In terms of mean pregnancy length and in terms of mean 1st and 5th min Apgar scores, the control group had significantly higher mean values (p=<0.001, for each comparison), while no statistically significant difference was found between the other two groups. In terms of mean HCT, PCT, MPV levels PP and PAS groups had significantly the lower mean values than control group (p=0.002, p=0.002, p<0.001, respectively), while no statistically significant difference was found between the PP and PAS groups. White blood cells (p<0.001), neutrophil count (p=0.005) and neutrophil-to-lymphocyte ratio (p=0.002) were found to be significantly higher, mean platelet volume (p<0.001) and plateletcrit levels (p=0.050) were significantly lower in the Placenta Previa group. Also, neutrophil-to-lymphocyte ratio (p<0.001) and platelet distribution width (p=0.027) were higher and lymphocyte count (p=0.021), mean platelet volume (p<0.001) and plateletcrit (p<0.001) levels were lower in the Placenta Accreta Spectrum group compared to the control group and the other intergroup differences were not statistically significant. There was no significant difference between placenta previa and placenta accreta spectrum groups except gravida and parity. The subgroup statistical analysis of the study population were shown in Table 2. In multivariate regression analyses, mean platelet volume (OR 4.01;95% CI 2.4–6.6), red blood cell (OR 3.12; 95% CI 2.72–3.56), and PDW (OR 0.22; 95% CI 0.17–0.28) were significantly associated with

Table 2. The subgroup statistical analysis of the study population

		Control -Placenta Previa	Control -PAS	Placenta Previa-PAS
Age (yr)	p	0.017	<.001	0.155
Gravidity	p	0.017	<.001	<.001
Parity	p	0.003	<.001	<.001
1-min-Apgar-score	p	<.001	<.001	1.000
5-min-Apgar-score	p	<.001	<.001	1.000
Hematocrit (%)	p	0.003	0.010	0.996
White blood cell, ×103/mm3	p	0.001	0.095	0.489
Neutrophil count, ×103/mm3	p	0.005	0.152	0.543
Lymphocyte count, ×103/mm3	p	0.346	0.021	0.231
Mean platelet volume(femtoliter)	p	<.001	<.001	0.994
Platelet distribution width (%)	p	0.540	0.027	0.244
Plateletcrit	p	0.050	0.001	0.124
Neutrophil-to-lymphocyte ratio	p	0.002	0.001	0.910

Table 3. Multivariate regression analysis for control and placenta previa groups.

Group	Predictor	p	95% CI for Odds Ratio		
			Odds ratio	Lower	Upper
Control Placenta Previa	Intercept	<.001	4.22e-23	4.18e-23	4.26e-23
	Red blood cell, ×106/mm3	<.001	3.12183	2.76552	3.52405
	Mean platelet volume (femtoliter) mpv	<.001	4.01902	2.44422	6.60846
	Platelet distribution width (%)	<.001	0.22288	0.17395	0.28558

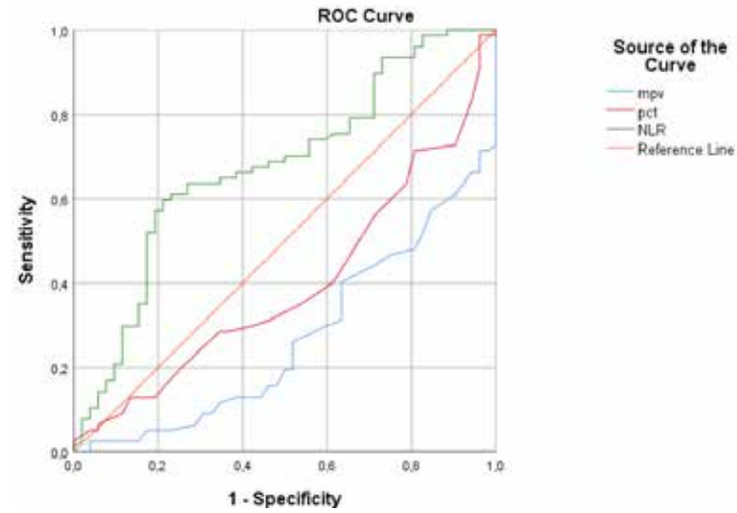

Figure 1. The ROC curve analysis of MPV, NLR, and PCT (PP–Control)

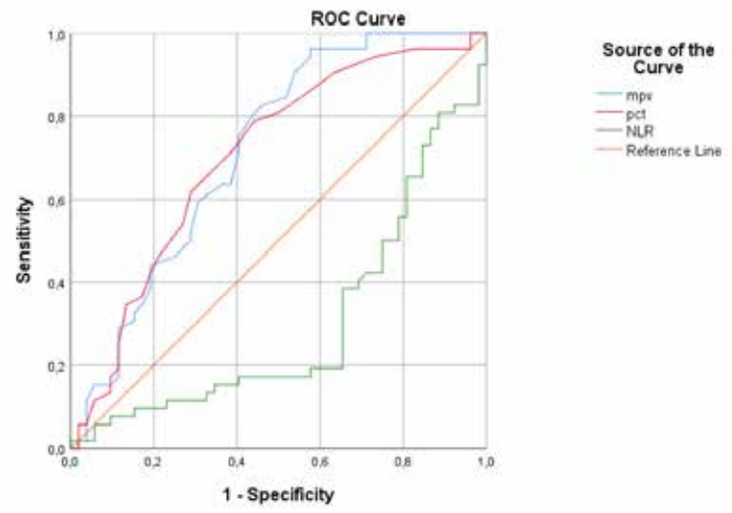

Figure 2. The ROC curve analysis of MPV, NLR, and PCT (PAS–Control)

the placenta previa (p<0.001) (Table 3).

In the receiver operating characteristic (ROC) analysis performed, the optimal MPV cut-off values to predict PP and PAS were respectively 9.95 (with a 63.5% sensitivity and 70% specificity, p<0.001) and 9.90 (63.5% sensitivity, 63.5.% specificity, p<0.001). The optimal NLR cut-off values to predict PP and PAS were respectively 4.47 (67.5% sensitivity, 58% specificity, p=0.001) and 4.45 (75% sensitivity, 57.7% specificity, p=0.001). The optimal PCT cut-off values to predict PP and PAS were respectively 0.205 (61.5% sensitivity, 62% specificity, p=0.047) and 0.205 (71.2% sensitivity, 61.5% specificity, p<0.001) (Figures 1 and 2).

Discussion

A healthy pregnancy requires controlled and programmed decidual trophoblast invasion as well as functional and adequate placentation. However, it is always possible that the invasion process may come to involve excessive trophoblast invasion in areas with inadequate vascularization, such as uterine scars. Studies have shown that placental trophoblasts might share similar proliferative, migratory, and invasive characteristics with cancer cells, acting as pseudomalignant or physiologically metastatic cells [10,11]. Controlled trophoblast proliferation depends on the balance between trophoblast survival and apoptosis [12-15]. In patients with PP or in the case of invasion, changes occur in the signal cascades producing extracellular stimuli, although trophoblasts do not undergo structural changes. This might be triggered by the loss of Nitabuch's layer or inflammatory conditions. The presence of natural killer and T lymphocytes and increase in lymphocytes and plasma cells at the placental adhesion area play a central role in such chronic inflammations [16].

Currently, there is no ideal prenatal method for predicting the heavy bleeding due to PP and PAS because the bleeding and blood loss volume depend on multiple factors, including the possible intraoperative complications of PP, which can lead to even higher morbidity and mortality. Although ultrasonography and prenatal magnetic resonance imaging have increased the rate of diagnosis by 90%, these facilities are still insufficient to determine the hemorrhagic blood loss volume [17]. Compared to intrapartum diagnosis, prenatal PAS diagnosis provides a reduction in maternal morbidity, as well as an opportunity for multidisciplinary approaches, preoperative planning, and direct medical care [18].

Cancer initiation, progression, and dissemination are affected by changes in the tumor microenvironment, as well as by the systemic immune and coagulation responses. In recent years, besides NLR, PLR, and MPV, various other non-invasive indicators, including lymphocyte-to-monocyte ratio, C-reactive protein, and absolute monocyte count, have been in use as systemic immune response markers in pathological inflammations and malignancies [19]. The inflammation due to angiogenesis, invasion, and metastasis leads to lymphocytosis, neutrophilia, thrombocytosis, and lymphocytopenia. The peripheral-blood NLR is a versatile marker used to evaluate the pre- and postoperative tumor invasion and cancer recurrence, establish the diagnosis of systemic and local inflammatory conditions such as prediabetes and diabetes, psoriasis, ulcerative colitis, rheumatoid arthritis, and Behçet's disease, and assess disease progression and the response to medical treatment [20].

Similarly, the PLR has gained widespread use as a laboratory marker to predict various neoplastic, prothrombotic, and metabolic diseases. In the case of a disease, this ratio may differ according to the underlying complex immuno-inflammatory responses, in positive correlation with the other markers of systemic inflammation, particularly the NLR. The PLR better predicts clinical outcomes in patients with systemic inflammation than platelet and lymphocyte counts alone [21].

In various studies, platelet markers and MPV as an indicator of early platelet activation have been associated with conditions involving thrombosis and inflammation. It has been reported that MPV may be increased in cardiovascular and cerebrovascular conditions and mild inflammation due to arterial and venous thrombosis and decreased in the case of diseases with severe inflammation, such as systemic lupus erythematosus, active rheumatoid arthritis, and inflammatory intestinal diseases. Increased platelet counts andplatelet aggregation facilitate tumor escape from the immune response [20,21].

Given that trophoblasts and tumor cells use similar pathways in the microenvironment in PP and PAS and that peripheral blood cells are involved in the inflammation process, this study aimed to evaluate the clinical utility of parameters for the antepartum detection of placental invasion anomalies. We reviewed the literature and found a limited number of relevant studies. In Yayla et al's [22] study using CBC parameters, patients with PP were divided into two groups based on the presence of invasion and it was found that MPV was significantly increased in patients with invasion compared to those without. In this study performed in 2016, which did not include a healthy control group, the increased MPV values in the invasion group might have indicated a low-grade inflammation. In our study, we precluded such effects on MPV through CBCs performed by using the same equipment and techniques within the first preoperative hour and, unlike the abovementioned study, the low MPV values that we measured in our PP group indicate the presence of high-grade inflammation.

In their case-control study, Ersoy et al. [23] compared CBC parameters between patients with PP and healthy controls in the first and third trimesters and found that total leukocyte and neutrophil counts and NLR values were significantly higher in the PP group only in the third trimester, while MPV values were found to be significantly lower. These results are consistent with those reported by Soylu et al. [24] in their retrospective study (2017), in which they compared PP patients with and without invasion anomalies and healthy controls and found that MPV values decreased in the invasion group of hysterectomized patients with a histopathological diagnosis of high-grade inflammation and invasion.

In the study by Taşgöz et al. [25] (2018) comparing participants with and without PP, it was found that only NLR and PLR values were significantly increased in the PP group, with no significant intergroup difference in MPV values. However, in our study, we observed that the mean MPV and PCT were significantly the highest in our control group, while there was no significant difference between the PP and PAS groups, regardless of the presence or absence of invasion. We also found that the mean

PDW, another platelet index, was the lowest in the control group. These results suggest that PP involves high-grade inflammation during which platelets undergo morphological and dynamic changes. As the inflammation intensifies, MPV decreases with a parallel increase in PDW due to the production of immature large platelets. Platecrit (PCT) is a parameter representing the volume of blood occupied by platelets, and decreased PCT values indicate hemostasis processes with no change in platelet mass.

Compared to the control group, our PP and PAS groups showed statistically significantly higher values of WBC and NLR with no significant difference between each other. In the PP group, which consisted of patients with no placental invasion anomaly, the mean NC was found to be significantly higher while the mean LC was lower. In consistence with the results reported by Ersoy et al. [23] and Soylu et al. [24], the NLR, PDW and NC increase and MPV, PCT, and LC decrease observed in our study show that these values as indicators of the systemic immune response are affected by the inflammatory process caused by trophoblastic activation in patients with PP. Again in accordance with the previous studies mentioned, we observed that the mean age, gravidity, parity and birth weight were quite higher in our PAS group, compared to the PP and control groups, while the mean pregnancy length and 1-5 minute Apgar scores were significantly higher in the control group. As reported in the literature, PP and PAS incidences are seen to increase in women with a higher parity [1].

Finally, it should be noted that our study has several limitations, the chief of which are its retrospective design and the small total sample size involved. Also, the size of the PAS group (n=52) was smaller than that of the PP group (patients with no PAS; n=77), and the absence of statistically significant differences between the two groups might have been caused by this.

Conclusion

In conclusion, our study demonstrated an inflammatory process in PP, where the placenta implants abnormally, using hematologic parameters independent of invasion depth. It was observed that these parameters (MPV) and ratios (NLR, Platecrit) from the complete blood count test used worldwide in primary health-care could contribute to the antepartum ultrasonographic diagnosis of this highly morbid and mortal pathology in the absence of magnetic resonance imaging facilities.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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