



Is there a change in platelet indices among pregnant with antiphospholipid syndrome?

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Abstract

Introduction: Recurrent pregnancy loss (RPL) is a common obstetrical complication, but 50% of cases have an undetermined etiology. Antiphospholipid syndrome (APL) is an autoimmune disease that has been linked to RPL. Platelet abnormalities, particularly thrombophilia, have been linked to RPL.

Objectives: This study examined the change in platelet parameters, specifically, platelet count, mean platelet volume (MPV), and platelet distribution width (PDW), in patients presenting with RPL caused by APL.

Patients and Methods: Fifty women with a confirmed diagnosis of APL syndrome with a history of RPL were assigned as a study group, and 50 women who gave birth without RPL were healthy controls. Pregnant women were recruited from Al Yarmouk teaching hospital. Personal data were collected through direct interviews with patients, followed by blood samples that were analyzed for complete blood counts and platelet indices.

Results: Both platelet count and PDW showed a significant correlation with the number of pregnancy losses; Pearson's correlation coefficient was ($r=0.74$, and $r=0.59$) for platelet count and PDW. The receiver operating characteristic (ROC) calculated a platelet count cut-off value of 230, with 88% sensitivity and 84% specificity, an area under the curve (AUC) of 0.89, and a P value of 0.001. The PDW had a cut-off value of 13.6 fl/L, associated with 88% sensitivity, 80% specificity, $AUC=0.87$, and a P value <0.001 .

Conclusion: Platelet indices may aid gynecologists in low-resource settings in predicting high-risk pregnancies deemed to suffer from RPL.

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Introduction

Recurrent pregnancy loss (RPL) is characterized as two or more unsuccessful clinical pregnancies under 20 weeks of gestation, as proven by ultrasound or histologic investigation, with the exclusion of ectopic pregnancies, hydatidiform mole, and chemical pregnancies. Up to 5% of women of childbearing age lose at least two conceptions in a row, while just 1% lose three or more (1). Early pregnancy loss is believed to affect 15% of all pregnancies, while losses between 12 and 22 weeks are less common, with a 4% incidence in all pregnancies. RPL has a complex etiology; in fact, the underlying etiology of 50%–60% of all RPL cannot be determined (2).

Antiphospholipid syndrome (APL) is a well-documented etiology for repeated pregnancy RPL (3), defined by thrombosis of the placental bed and increased maternal morbidity in the presence of positive maternal anti-phospholipid antibody biomarkers (4). APL affects 3–5% of the general population and is the most commonly acquired risk

Key point

This study explored the reasons for poor outcomes in patients with confirmed APL presented with RPL. In addition to the auto-antibodies that were accredited for the unfavorable obstetrical outcome in ACL patients, this study examined the platelet changes seen among affected cases and verifies their role in RPL pathogenesis.

factor for thrombophilia (5). Aspirin and heparin were used to treat cases of APL in order to reduce the bad obstetrical effects, such as RPL (1). Though APL was linked to autoantibodies, recent studies suggest that platelet indices play a role in its pathogenesis (6).

Due to the feasibility of a complete blood picture and its components, including platelet indices, that made them a pleasant and inexpensive option for screening in RPL cases (7).

Thrombophilia in pregnancy affects placenta development, and failure to implant the fertilized egg in the uterine decida



has been proposed as a cause of early pregnancy loss, especially between the twelfth and fourteenth weeks (8). Pregnancy is a hypercoagulability state where multiple alterations occur in the blood (like platelet changes) to ensure healthy implantation and successful pregnancy outcomes (9). In earlier studies, the underlying pathology of RPL was linked to changes in platelet counts and indices (mean platelet volume [MPV] and platelet distribution width [PDW]). The MPV represents the mean size of platelets in the circulation. Increased platelet production is linked to a high MPV. The MPV ranges between 6.8 and 10.4 fL on average. Platelet PDW is an indicator of platelet anisocytosis. The standard PDW is between 9 and 14 fL. These indices were used as screening and prognostic parameters (7).

Objectives

This study compared platelet parameters, such as platelet count, MPV, and PDW, in patients with RPL who have a confirmed APL diagnosis versus healthy control.

Patients and Methods

Study design

This case-control study was conducted at the fertility clinic of Al Yarmouk teaching hospital from January 2020 to January 2021.

A total of 100 eligible pregnant women were recruited, divided into 50 women with a history of RPL (2 or more) due to APL; assigned as a study group, and 50 healthy controls who had given at least one live birth without RPL. To confirm the laboratory diagnosis of APL, we need to detect antibodies such as anti-cardiolipin antibodies or lupus anticoagulants in two or even more instances at least three months apart. Women in the study were between 20 and 35 years old, in their first trimester of a singleton pregnancy, confirmed by their last menstrual period and an early date ultrasound. Patients with a history of

chronic illnesses, fever, confirmed infection, immobility, surgical intervention, uterine deformities, smokers, and those using non-steroid anti-inflammatory medications or anticoagulants were excluded. We enrolled patients that had not started any treatment, i.e., neither aspirin nor heparin. For all participants, we collected demographic data, age, body mass index (BMI), and abortion numbers. Blood samples were collected into tubes containing K3EDTA and samples were evaluated within two hours. Blood samples from the RPL group were taken as soon as possible, and a complete blood picture using the Abbott Cell Dyn 3500 CS was done, where platelet counts, MPV, and PDW were calculated and recorded on excel sheets.

Statistical analysis

Continuous data were expressed as mean \pm SD, and the Shapiro-Wilk test was used to determine data normality. A student *t* test was used to compare the different means and SD between study cases and healthy controls. Pearson's coefficient of correlation assessed the relationship between platelet indices and abortion numbers. The ROC curve evaluated the cut-off value for platelets counts and PDW. The analysis was conducted by MedCalc version 20. For all tests, *P* values of 0.05 was significant.

Results

We conducted a case-control study on 100 pregnant women. Table 1 describes the main demographic criteria for both study subgroups. No significant differences were found regarding age, BMI, and hemoglobin. Each platelet counts and PDW were significantly higher in ACL cases versus healthy controls, while MPV failed to show statistical significance. Table 2 demonstrates Pearson's correlation between abortion numbers taken as an independent variable versus platelet counts, PDW, and MPV. Only MPV showed no meaningful correlation with an insignificant *P*-value. On the other hand, platelet counts

Table 1. The primary demographic criteria of the study participants

Parameter	Study group Mean \pm SD, n = 50	Healthy controls Mean \pm SD, n = 50	<i>P</i> value
Age (y)	30.0 \pm 6.86	29.08 \pm 7.41	0.71
Body mass index (kg/m ²)	26.21 \pm 3.6	25.27 \pm 2.67	0.16
Hemoglobin (g/dL)	11.39 \pm 1.18	11.80 \pm 1.21	0.23
Platelets counts ($\times 10^9/L$)	307.84 \pm 67.90	209.40 \pm 33.74	0.0001*
Platelets distribution (width/L)	15.71 \pm 1.53	12.23 \pm 2.25	0.0001*
Mean platelets volume (fL)	10.41 \pm 1.19	9.93 \pm 0.95	0.120

*indicate statistically significant values.

Table 2. Pearson's correlation between abortions number versus platelets indices

Parameters	Pearson's correlation (<i>r</i>)	<i>P</i> value
Abortion No. versus platelets count	0.74	<0.001*
Abortion No. versus PDW	0.59	<0.001*
Abortion No. versus MPV	0.2	0.173

PDW; platelets distribution width, MPV; mean platelet volume. *indicate statistically significant values.

Table 3. Highlights the cut-off values, sensitivities, specificities and respective *P* values for platelets counts and PDW estimated by the ROC curve

Parameters	Sensitivity	Specificity	Cut-off value	AUC	<i>P</i> value
Platelets counts	88	84	>230	0.890	<0.001*
PDW	88	80	>13.6	0.878	<0.001*

PDW, platelet distribution width. *indicate statistically significant values.

and PDW showed a significant correlation as $r=0.74$ and $r=0.59$, respectively. Table 3 describes the ROC curve used to calculate the cut-off value, sensitivity, specificity, AUC, and *P* values for platelet counts and PDW. A cut-off value of 230 for the platelet counts showed a sensitivity of 88%, specificity of 84%, AUC=0.89, and a *P* value <0.001. The PDW had a cut-off value of 13.6 fl/L, associated sensitivity and specificity of (88%, and 80%) respectively, AUC: 0.87, *P* value <0.001 in predicting RPL.

Discussion

This study highlighted platelet changes in pregnant women with confirmed APL syndrome versus matched controls in the first trimester. Both platelet counts and PDW were meaningfully higher in APL cases versus healthy controls. A trend of higher MPV was found in cases versus controls. Still, it fails to reach a statistical value.

Our result contradicts other studies that confirmed insignificant PDW among ACL patients versus healthy pregnant women (10). On the other hand, Lood et al study (11) discussed a significantly lower MPV volume in APL cases than in the general population. This volume variation was attributed to platelet activation that is caused by released inflammatory cytokines (12,13). Lood et al study presented a novel finding and introduced an exciting concept; in contrast to the general population, reduced MPV is associated with a higher thrombosis risk in APL syndrome cases (11).

Platelets count in our study were significantly higher in ACL cases versus healthy controls. Avcioglu et al recommended platelet indices among RPL cases for routine testing, although their study found insignificant differences regarding all platelet parameters, including platelet counts (14).

In line with our analysis, platelets' count and indices were meaningfully high in RPL cases compared to healthy pregnant women in the Al-Aghbary et al study (15).

The platelets distribution width was significantly higher in our analysis at $P<0.0001$, in line with Vinatier et al (10), Lood et al (11), Al-Aghbary et al (15) studies and in contrast to Avcioglu et al (14).

Zhao et al investigated 207 patients (135 females and 72 males) subdivided into thrombotic and non-thrombotic cases. Both PDW and MPV were meaningfully high in ACL cases versus controls ($P<0.001$). By using logistic regression, PDW and MPV were strongly linked to the risk of thrombosis in APL cases. In addition, the ROC curve confirmed that the PDW cut-off value of 12.41 fl was associated with 72%,77.2% sensitivity, and specificity,

respectively, AUC of 0.79 in predicting the thrombotic risk. Therefore, they suggested platelet activation as a critical element for thrombosis in ACL cases (16).

The ROC curve in our analysis showed good performance for both platelet counts and PDW by comparing their respective AUC (0.89, and 0.87) respectively.

The hematological system plays a vital role in the success of early implantation. RPL may be attributed to placental micro-infarctions initiated by increased platelet numbers (17,18). The high platelet counts cause platelet aggregation, increased blood viscosity, and tissue hypoxia. The latter causes the release of inflammatory mediators that will cause platelets activation. Activated platelets lead to thromboxane production, which induces platelet aggregation, leading to the placental bed's microvascular thrombosis, consequently resulting in abortion (19). Those mentioned above are the primary underlying pathological basis of first-trimester abortion in patients with RPL, in addition to the effect of autoantibodies in APL cases, which initiate placental damage (17-20).

The value of platelets in obstetrical practice was further investigated in early implantation failure, pre-eclampsia, fetal growth restriction, and other poor pregnancy outcomes (21-23). Nevertheless, they still showed inconsistent results; their feasibility and low-cost warrant further research exploring different implications in obstetrics and gynecology. The current study's small sample size may limit its implications. However, a prospective study conducted in a single center allowed us to carefully recruit and examine all blood tests, a point of strength for the current research.

Conclusion

Platelet count and PDW had significant correlations with abortion numbers in ACL cases with good discrimination power; ACL is a common cause of RPLs. Complete blood counts may help gynecologists, particularly in low-resource settings, detect high-risk pregnancies deemed to have RPL.

Limitations of the study

Small sampling size and a lack of power of analysis are the main limitations.

Authors' contribution

Conceptualization: WN and SKH.

Methodology: RMH and WN.

Validation: SKH.

Formal analysis: WN.

Investigation: WN and RMH.

Resources: RMH.

Data curation: RMH.

Visualization: SKH

Writing-original draft: WN and SKH.

Writing-review and editing: WN.

Supervision: WN.

Project administration: WN.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical issues

The research followed the tenets of Helsinki Declaration. The ethics committee of Al-Mustansiriyah, faculty of medicine issued its approval (Ref# 149 at 22-4-2020). A written informed consent was taken from all participants before embarking into the study. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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