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

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The study complies with current ethical considerations.

Key point

Although many physicians adhere to the recommendation of managing antiphospholipid syndrome (APL), some patients still suffer from bad outcomes.

Platelets changes associated with cases of recurrent pregnancy loss (RPL) were examined for a possible association.

Abstract

Introduction: Recurrent pregnancy loss (RPL) is a common obstetrical complication, where 50% have undetermined etiology. Antiphospholipid syndrome (APL) is an autoimmune disease documented as a cause of RPL. Thrombophilia, particularly platelet abnormalities, were accredited for RPL.

Objectives: this study determines the change in platelets parameters; specifically, platelet count, mean platelet volume (MPV), platelet distribution width (PDW), in patients suffering from RPL caused by the anti-phospholipid syndrome.

Patients and Methods: Fifty women with a confirmed diagnosis of APL syndrome having a history of RPL were assigned as a study group and fifty women who gave birth without RPL were set as healthy controls were taken from Al Yarmouk teaching hospitals in Baghdad. The personal data were taken by direct interview with patients,
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then blood samples were taken and analyzed for complete blood counts and platelets indices.

**Results:** Both platelets count and platelet distribution width (PDW), scored significant correlation with the number of pregnancy loss; Pearson's correlation coefficient was (0.74,0.59) respectively for both variables. The ROC (receiver operating characteristic) evaluated platelets count cutoff value of 230 , with respective sensitivity of 88%, specificity of 84%, area under curve (AUC) =0.89, and P-value<0.001. As for PDW it had a cutoff value of 13.6 fl/L, associated sensitivity of 88%, specificity of 80% , AUC=0.87, and P-value<0.001.

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

**Keywords:** Antiphospholipid syndrome, Recurrent pregnancy loss, Mean platelets volume ,Platelets distribution width

**Introduction**
Repeated pregnancy loss (RPL) is characterized as 2 or more unsuccessful clinical pregnancies under 20 weeks of pregnancy, as proven by ultrasound or histologic investigation, excluding ectopic pregnancies, hydatidiform mole, and chemically 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 of all pregnancies. Thus, RPL has a complex etiology. Nevertheless, in 50%–60% of all RPL, the underlying etiology cannot be determined (2).

Autoimmunity is another well-documented aetiology for repeated pregnancy RPL, (3); notably, antiphospholipid syndrome (APL) is defined by thrombosis of the placental bed and increased maternal morbidity in the presence of positive maternal morbidity anti-phospholipid antibody biomarkers (4). Antiphospholipid syndrome has an incidence of 3-5 per cent in the overall population, and it is the most commonly acquired risk parameter for thrombophilia (5). In managing APL, aspirin and heparin were implemented to decrease the poor obstetrical consequences linked with APL, including RPL (1). Though APL was accredited to autoantibodies, recent studies suggested that platelets indices play a role in its pathogenesis (6).
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Therefore, the feasibility of a complete blood picture and its component, including platelets indices, made them a pleasant and inexpensive option for screening (7). Thrombophilia in pregnancy affects placenta development, and implanting the fertilized egg in the uterine decidua 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 to ensure healthy implantation and successful pregnancy outcomes like platelets changes (9). Earlier studies correlated changes in platelet counts and indices mean platelets volume (MPV) and platelets distribution width (PDW) to the underlying pathology for RPL. The mean size of platelet cells in the circulation is described by the mean platelet volume (MPV), which is a device measurement. Increased platelet generation is linked to a high MPV. The MPV ranges between 6.8 and 10.4 fL on average. An indicator of platelet anisocytosis is the platelet PDW. The standard PDW is between 9 and 14 fL. Therefore, these indices were used as screening and prognostic parameters (7).

Objectives

This study compares 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- January 2021. A total of 100 consented pregnant women were recruited for this study, divided into 50 women with a history of RPL (2 or more) confirmed to have APL assigned as a study group and 50 healthy controls who had given at least live birth without RPL. To confirm APL diagnosis, we need to detect antibodies such as anti-cardiolipin antibodies or lupus anticoagulants on two or even more instances at least three months apart for its laboratory diagnosis. Women in the study were between 20 and 35 years old, in their first trimester of a singleton pregnancy, as verified 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
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enrolled patients that did not start any treatment, i.e. neither aspirin nor heparin. For all participants, we collected anthropometric data, age, body mass index, and abortion numbers. The antecubital vein was used to collect blood samples. Tubes containing K3EDTA were used, 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 platelets counts, MPV and PDW were calculated and recorded on excel sheets.

Statistical analysis

Continuous data were expressed as Means ±SD, Shapiro-Wilkinson test checked the data normality. Un paired T-test was used to compare the different means and SD between study cases and healthy controls. Pearson’s coefficient correlation assessed the relation between platelet indices versus abortion numbers. The ROC curve evaluated the cutoff value for platelets counts and PDW. Analysis was conducted by MedCalc version20. P-value <0.05 was significant for all tests.

Results

To 100 pregnant women, we conducted a cases control study (Table 1). Illustrated the primary demographic criteria for both study sub-groups. No significant differences were found regarding age, BMI, and hemoglobin. Both platelets counts and PDW scored significantly higher in cases versus healthy controls, while MPV failed to show statistical significance. Table 2 demonstrate Pearson's correlation between abortion number taken as independent variable versus platelets counts, PDW, and MPV. Only MPV showed no meaningful correlation with nominal P-value. On the other hand, both platelets counts and PDW scored significant correlation as $r=0.74$, and 0.59 respectively. The ROC curve was constructed to estimate cutoff value, sensitivity, specificity and AUC with respective P-values shown in Table 3. For platelets count a cutoff value of 230 showed a sensitivity of 88%, specificity of 84%, AUC=0.89, and P-value<0.001. As for PDW, it had a cutoff value of 13.6 fl/L, sensitivity of 88%, specificity of 80%, AUC=0.87, and P-value<0.001.

Discussion
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This study highlighted platelets changes observed at the first trimester in patients with confirmed APL syndrome versus matched controls. Both platelets counts and PDW scored meaningfully higher in cases versus healthy controls. A trend of higher PDW was observed in cases versus controls. Still, it fails to reach a statistical value of \( P > 0.05 \).

Our result contradicts other studies that confirmed significant higher PDW among patients versus healthy pregnant women, with a value of 10.2 ± 2.1, P-value <0.001(10). On the other hand, Lood et al. study discussed a significantly lower MPV \( P < 0.003 \) volumes in APL cases than the general population. These volumes variation was attributed to platelets activation that is caused by released inflammatory cytokines. (11,12). Their study presented this novel finding and introduced an exciting concept; in contrast to the general population, reduced MPV is associated with higher thrombosis risk in APL syndrome cases (13). Platelets counts were significantly higher in cases versus healthy controls based on our analysis. Conversely, Avcioğlu et al. recommended platelets indices among RPL cases for routine testing, although their study found non-meaningful differences regarding all platelets parameters, including platelets counts (14).

In line with our analysis, platelets' count and indices were meaningfully high in RPL cases compared to healthy pregnant in Al-Aghbary et al. study (15). The platelets distribution width scored significantly higher in our analysis as \( P < 0.0001 \), In line with Abuelela, Lood, Al-Aghbary studies and in contrast to Avcioğlu(12-15). Zhao et al investigated 207 patients (135 female and 72 males) subdivided into thrombotic and non-thrombotic cases. PDW, MPV, were meaningfully high in cases versus controls, \( P < 0.001 \). By logistic regression, PDW and MPV showed a significant association with the thrombosis risk among APL cases. However, the ROC curve confirmed that the PDW cutoff 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 recommended platelets activation as a critical element for thrombosis in ACL cases (16).

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

The hematological system plays a vital role in the success of early implantation. RPL may be attributed to placental micro-infarctions triggered by increased platelet numbers. The high platelet counts cause platelet aggregation, increased blood viscosity and tissue hypoxia. The latter causes release of inflammatory mediators that will render
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the platelets active. Activation of platelets leads to thromboxane production, which induces platelet aggregation, leading to the placental bed's microvascular thrombosis, consequently resulting in abortion. Besides the effect of autoantibodies in APL cases which initiate placental damage, these are the primary underlying pathological basis of first-trimester abortion in patients with RPL (17-20). The value of platelets in obstetrical practice was further investigated in early implantation failure, preeclampsia, 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 gynaecology. The current study has a small sampling size, which may limit its implications. However, a prospective study conducted in a single centre allowed us to carefully recruit and examine all blood tests, a point of strength to the current research.

Conclusion

Platelets count and PDW scored significant correlations with abortion numbers in ACL cases; ACL is a common cause of recurrent pregnancy losses. The availability of complete blood counts may help gynaecologists, particularly in low-resource settings, to detect high-risk pregnancies deemed to have RPL.

Limitations of the study

Small sampling size and lacking power of analysis are the main limitation.

Authors’ contribution

WN, SKH and RMH were the principal study investigators. WN, and SKH were equally responsible for the study concept and generation of its design. WN and RMH revisited the manuscript and reviewed its intellectual contents. All authors took part in preparing the final draft of the manuscript, manuscript revision and critically evaluated the scientific contents. All authors have read and agreed to the content of the manuscript and confirmed the integrity of all study parts.

Conflicts of interest

The author declares no conflicts of interest.
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Ethical issues

The research followed the tents 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, double publication) have been completely observed by the authors.

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None

References


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Table 1. The primary demographic criteria of the study participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study group Mean±SD, N=50</th>
<th>Healthy controls Mean±SD, N=50</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.0±6.86</td>
<td>29.08±7.41</td>
<td>0.71</td>
</tr>
<tr>
<td>Body mass index(kg/m²)</td>
<td>26.21±3.6</td>
<td>25.27±2.67</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin g/dl</td>
<td>11.39±1.18</td>
<td>11.80±1.21</td>
<td>0.23</td>
</tr>
<tr>
<td>Platelets counts (×10⁹/L)</td>
<td>307.84±67.90</td>
<td>209.40±33.74</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Platelets distribution width/L</td>
<td>15.71±1.53</td>
<td>12.23±2.25</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Mean platelets volume fl/L</td>
<td>10.41±1.19</td>
<td>9.93±0.95</td>
<td>0.120</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pearson’s correlation (r)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortion No. versus Platelets count</td>
<td>0.74</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Abortion No. versus PDW</td>
<td>0.59</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Abortion No. versus MPV</td>
<td>0.2</td>
<td>0.173</td>
</tr>
</tbody>
</table>

PDW; Platelets distribution width, MPV: Mean platelets volume

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cut-off value</th>
<th>AUC</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets counts</td>
<td>88</td>
<td>84</td>
<td>&gt;230</td>
<td>0.890</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PDW</td>
<td>88</td>
<td>80</td>
<td>&gt;13.6</td>
<td>0.878</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

PDW; Platelets distribution width
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