

# The Association Between Platelet Indices and Clinical Parameters in Recurrent Pregnancy Loss

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**OBJECTIVE:** Etiology of recurrent pregnancy loss (RPL) is variable. Hypercoagulability is one of the treatable conditions causing RPL. Platelet (PLT) count, mean PLT volume (MPV), PLT distribution width (PDW) and plateletcrit (PCT) are platelet indices and may be markers for increased platelet aggregability. In the present study, we aimed to determine and compare PLT count, MPV, PDW and PCT between patients with RPL and healthy controls.

**STUDY DESIGN:** A total number of 39 patients with RPL and 40 healthy controls were enrolled in the research. PLT count, MPV, PDW and PCT values were compared between the patients and the controls.

**RESULTS:** There were no statistically significant differences in number of PLTs, MPV, PCT and PDW values between women with RPL and healthy women ( $p > 0.05$ ).

**CONCLUSION:** Thrombocyte indices have still an unsatisfactory value in RPL and it seems that they are not appropriate for routine clinical practice regarding RPL.

**Keywords:** Recurrent pregnancy loss, Platelets, Mean platelet volume, Platelet distribution width, Plateletcrit

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## Introduction

Recurrent pregnancy loss (RPL) is a very important public health problem. In addition to psychological trauma to the mother and the family, it is associated with maternal morbidity and mortality.<sup>1</sup> This serious condition affects about 1-5% of pregnant women.<sup>2</sup> In the literature, there is no consensus on the number of pregnancy losses needed to make the diagnosis of RPL. According to guidelines from European Society of Human Reproduction and Embryology (ESHRE), RPL is three or more consecutive pregnancy losses before 22 weeks of gestation.<sup>3</sup> It is classically defined in the literature as three or more spontaneous fetal losses before the 20<sup>th</sup> week of pregnancy,<sup>4</sup> but in some studies, two or more losses were considered sufficient to diagnose RPL.<sup>5</sup> The probability of abortion

following three consecutive losses in the first trimester rises with increased maternal age; the incidence of RPL is 25% in women aged  $\geq 30$  years and it may increase to almost 50% in those aged 40 years.<sup>6</sup> RPL is a multifactorial disease. Uterine malformations, endocrine diseases such as hypopituitarism and diabetes, infectious diseases, genetic alterations like chromosomal aberrations and inflammatory diseases including systemic lupus erythematosus are blamed for etiology of RPL.<sup>7,8</sup> However, about 20-80% of all cases still remain unexplained.<sup>9</sup>

There have been many studies showing that oxidative-inflammation caused by immune mechanisms and thrombosis is responsible for pathogenesis of RPL.<sup>10,11</sup> However, the role of platelets (PLTs) in these pathways still is not known completely. Mean PLT volume (MPV), PLT distribution width (PDW) and plateletcrit (PCT) are platelet indices. In the present research, we aimed to compare changes in PLT count, MPV, PDW and PCT between patients with RPL and healthy controls.

## Material and Method

The current study comprised patients who presented to Gynecology clinics of Adnan Menderes University Hospital. The Complete Blood Count (CBC) and clinical findings of these patients were evaluated. Permission was granted by

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The study included 39 women with at least two subsequent miscarriages and a control group of 40 women who gave birth without experiencing any miscarriages. Patients presenting to the hospital with liver and kidney disease, additional systemic inflammatory disease, high fever or infection history within the previous five days, myeloproliferative disease, or malignancy were excluded from the study. Besides, the women who smoked and those who took oral anticoagulants or oral contraceptives, anti-inflammatory drugs, acetylsalicylic acid, likely to affect PLT count and functions or the coagulation system, were also excluded from the study. For automatic blood count, EDTA tubes (15% K3 EDTA 0.054ml/4.5 ml blood) were used. All CBC analyses were performed with the same analyzer, Mindray BC 6800 (M68 LH LYSE, China), within 2 hours after collection of blood samples in the haematology laboratory of our hospital. Haematological parameters which consisted of PLT count ( $156\text{-}373 \times 10^9/\text{L}$ ), MPV (7.4-10.4 fL), PDW (15.6-18.2 fL) and PCT (0.155-0.320%) were analyzed by standard methods.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) for Windows (Version 18.0). Descriptive analyses were presented using means and standard errors of mean (SEM) for normally distributed variables. The Student's t-test was used to compare these parameters between the RPL and control groups. Correlations were studied using Pearson's correlation test.  $p < 0.05$  was regarded as statistically significant.

## Results

The study comprised a total of 79 women; 39 with repeated miscarriages and 40 healthy women. The mean age of the women was  $30.28 \pm 4.58$  years (21-37 years) in the RPL group and  $32.20 \pm 3.74$  years (23-38 years) in the control group. Totally, there were 24 women (30.4%) aged  $< 30$  years and 55 women (69.6%) aged  $\geq 30$  years. The mean number of previous miscarriages in the RPL group was  $2.77 \pm 1.03$  ranging from 2 to 8. Sixteen women (41%) had two abortions, 20 women (51.3%) had three abortions, two women (5.1%) had 4 abortions and one woman (2.6%) had 8 abortions on their obstetric history. Twenty seven women (69.2%) had their first abortion in  $< 12$  weeks of gestation and 12 women (30.8%) had their first abortion after 12 weeks of gestation. Besides, 26 women (66.7%) had their second abortion in  $< 12$  weeks of gestation and 13 women (33.3%) had their second abortion after 12 weeks of gestation. There was not a difference between the patients with RPL and the control group in terms of age, PLT counts, MPV, PCT and PDW. The MPV values of the RPL and control groups were  $8.42 \pm 0.83$  and  $8.67 \pm 1.31$  re-

spectively, and there was not a statistically significant difference between the groups ( $p=0.33$ ). The PDW values for the groups were  $16.59 \pm 0.53$  and  $16.71 \pm 0.77$  respectively, and there was not a significant difference between the groups ( $p=0.44$ ) (Table 1). In addition, PLT, PCT, MPV and PDW values did not differ between patients who had abortions in the first trimester ( $< 12$  weeks) and those who had abortions in the second trimester ( $\geq 12$  weeks) ( $p > 0.05$ ).

In present study, there was not a significant correlation between the number of miscarriages and MPV, PDW and PCT values ( $P$  0.28, 0.36 and 0.22 respectively). In the RPL group, the only statistically significant correlation was determined between age and the number of abortions ( $p=0.04$ ).

Table 1: Comparison of clinical parameters between patients with RPL and controls

	RPL <sup>1</sup> (n=39)	Controls (n=40)	p
Age (years)	$30.28 \pm 4.58$	$32.20 \pm 3.74$	0.46
PLT <sup>2</sup>	$261.36 \pm 59.37$	$275.83 \pm 57.31$	0.27
MPV <sup>3</sup>	$8.42 \pm 0.83$	$8.67 \pm 1.31$	0.33
PCT <sup>4</sup>	$0.21 \pm 0.04$	$0.23 \pm 0.52$	0.09
PDW <sup>5</sup>	$16.59 \pm 0.53$	$16.71 \pm 0.77$	0.44

RPL<sup>1</sup>: Recurrent pregnancy loss, PLT<sup>2</sup>: Platelet, MPV<sup>3</sup>: Mean platelet volume, PCT<sup>4</sup>: Plateletcrit, PDW<sup>5</sup>: Platelet distribution width

## Discussion

In the present study, platelet indices including MPV, PCT and PDW, which were also physiological parameters of haemostatic importance, have been investigated in patients with RPL. We found no significant differences in MPV, PCT and PDW values between the women with RPL and the healthy controls, which is consistent with the literature.<sup>12,13</sup>

It is known that the haemostatic system plays an important role in the success of implantation and placentation. The implantation of the embryo into the uterine deciduas depends on a compatible interaction between the placenta, fetus and maternal circulation. Therefore, the contact between the placenta and maternal circulation is very important for the success of the pregnancy.<sup>14</sup> Abnormal placentation in the first trimester leading to oxidative stress and resultant endothelial dysfunction plays a key role in the complications of pregnancy such as abortions.<sup>15</sup> There are many reports in the literature indicating that thrombotic and inflammatory processes play a major role in abnormal placentation and spontaneous abortion. It has been shown that tumor necrosis factor alpha (TNF- $\alpha$ ) and interferon gamma (IFN- $\gamma$ ) are important cytokines inducing thrombotic/inflammatory pathways in maternal uteroplacental blood vessels and causing abortions.<sup>16</sup>

PLTs play an important part in the pathogenesis of vascu-

lar diseases.<sup>17</sup> The MPV test is an indicator of PLT size.<sup>18</sup> It has been reported that MPV is a reflection of both proinflammatory and prothrombotic conditions like RPL.<sup>19</sup> Increased MPV indicates that PLT diameters are greater. An increase in MPV shows that new PLT synthesis in the bone marrow has increased. Thus bigger, younger and more functional PLTs are produced as MPV increases. Young and big PLTs produce more prothrombotic factors and groups more easily.<sup>18</sup> Several prospective studies and a meta-analysis have suggested a correlation between an increase in MPV and the risk of thrombosis.<sup>19</sup>

On the other hand, low levels of MPV have been detected in high-grade inflammatory diseases, such as active rheumatoid arthritis or attacks of familial Mediterranean fever. It is frequently reported that there is an inverse relationship between PLT count and MPV, reflecting the tendency to maintain hemostasis by preserving a constant PLT mass.<sup>20</sup> This inverse relationship is often seen in inflammatory disorders. In these conditions, enhanced thrombopoiesis increases the quantity of circulating PLTs, and a large amount of highly reactive large PLTs migrate to inflammatory sites, where they are intensely consumed.<sup>21</sup>

PDW and PCT are other and often omitted indices of PLT. Clinicians generally pay less attention to these than to PLT count and MPV. PCT is a measurement derived from the PLT count and the MPV. It was accepted as an indicator of circulating PLTs in a unit volume of blood.<sup>22</sup> PDW is a direct flow cytometric measurement of PLT cell volume.<sup>23</sup> As PDW does not increase with PLT distension, it is considered as a more specific marker of PLT activation than MPV. It has been suggested that MPV and PDW together are more meaningful for coagulation activation.<sup>24</sup>

In the current study, contradictory effects of proinflammatory and prothrombotic pathways blamed for RPL might have caused stability in the number and dimensional characteristics (MPV, PCT, PDW) of PLTs in maternal blood. Another issue explaining the stable count and dimensional characteristics of PLTs in RPL might be sticky PLT syndrome (SPS), as reported by Bick et al. It was the second most common prothrombotic defect contributing to RFL associated blood coagulation protein/PLT defect.<sup>25</sup> SPS was a PLT disorder associated with arterial and venous thromboembolic events. It is characterized by hyperaggregability of PLTs due to rich plasma with adenosine diphosphate (ADP) and epinephrine (type I), epinephrine alone (type II) or ADP alone (type III).<sup>26</sup>

In conclusion, although it is known that hypercoagulation and PLT activation have caused morphological changes in PLTs, contradictory effects of proinflammatory factors and hypercoagulopathy have been held responsible for stability of these indices in pathogenesis of RPL. Therefore, thrombocyte

indices have an unsatisfactory value in RPL and may not be used in clinical practice concerning RPL. However, the present study, which focused on PLT indices in RPL, was just a preliminary study. Molecular, genetic and immunohistochemical studies about the PLT cell structure are essential to understand their roles in RPL.

## Tekrarlayan Gebelik Kayıplarında Trombositlerin Rolü Nedir?

**AMAÇ:** Tekrarlayan gebelik kayıplarına (TGK) neden olan faktörler çeşitlilik göstermektedir. Hiperkoagülasyon TGK'na sebep olan ve tedavi edilebilen etkenlerden biridir. Platelet (PLT) sayısı, ortalama PLT hacmi (MPV), PLT dağılım aralığı (PDW) ve PLT crit trombosit indeksleridir ve artmış trombosit agregasyonunun parametreleri olabilirler. Bu çalışmada amaç, TGK olan hastalarda ve sağlıklı bireylerde PLT sayısı, MPV, PDW ve PCT değerlerinin saptanması ve karşılaştırılmasıdır.

**GEREÇ VE YÖNTEM:** Çalışmaya TGK olan 39 hasta ve 40 sağlıklı kadın alınmıştır. Tüm katılan bireylerde PLT sayısı, MPV, PDW ve PCT değerleri karşılaştırılmıştır.

**BULGULAR:** Sağlıklı konrollerle karşılaştırıldığında, TGK olan kadınlarda PLT sayısı, MPV, PDW ve PCT değerlerinde herhangi bir istatistiksel anlamlı fark saptanmamıştır. ( $p>0,05$ )

**SONUÇ:** Trombosit indeksleri TGK olan hastalarda henüz tatin edici değere sahip değildir ve klinik pratikte rutin olarak kullanılması pek uygun gibi gözükmemektedir.

**Anahtar Kelimeler:** Tekrarlayan gebelik kaybı, Platelet sayısı, Ortalama platelet hacmi, Platelet dağılım aralığı, Platelet crit

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