Relationship between mean platelet volume and recurrent miscarriage: a preliminary study

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Abstract

Introduction: The aim of the study was to examine the relationship between mean platelet volume (MPV) and recurrent miscarriage in order to illuminate the etiopathogenesis of recurrent miscarriage.
Material and methods: We retrospectively investigated the data of 120 patients with unexplained recurrent miscarriage (group 1), and compared them with the data of 120 match-paired patients in the control group (group 2). The definition of recurrent miscarriage was accepted as two or more failed clinical pregnancies which were documented by ultrasonography or histopathologic examination. All patients in the recurrent miscarriage group were evaluated with diagnostic tests for the etiology of recurrent miscarriage. Total blood count parameters, including hemoglobin, mean corpuscular volume, red cell distribution width, white blood cells, platelets, and mean platelet volume, were compared.
Results: The average patient age at the time of examination was 29.07 ±2.81 years in group I and 28.53 ±3.5 years in group II ($p > 0.05$). Mean body mass index (BMI) was similar between group 1 and group 2, 22.54 ±3.17 and 22.99 ±2.38, respectively ($p > 0.05$). Mean hemoglobin, mean corpuscular volume, red cell distribution width, and white blood cell and platelet levels were similar in both groups ($p > 0.05$). Mean platelet volume levels were significantly higher in group I (9.45 ±1.09 fl) than in group II (7.63 ±0.52 fl) ($p = 0.001$).
Conclusions: Higher MPV values in the study group suggest and support the importance of thromboembolic events in the etiology of recurrent miscarriage.

Key words: recurrent miscarriage, mean platelet volume, thrombophilia.

Introduction

Recent evidence indicates that two or more, not necessarily consecutive, miscarriages constitute recurrent miscarriage [1]. Recurrent miscarriage affects 1% of couples trying to conceive. Etiology is not identified in half of the cases [2]. Parental chromosomal anomalies and thrombotic complications constitute two of the most common known causes of recurrent miscarriage [3].

Thrombophilia, which is a condition with an increased tendency to venous thrombosis, is associated with recurrent miscarriage. Micro-emboli in the uteroplacental circulation, which lead to placental insufficiency and inflammation, are considered to cause recurrent miscarriage in pregnant women with thrombophilia [4].

Mean platelet volume (MPV) is an important risk factor for the development of atherothrombosis and embolism [5]. Increased MPV has been defined as an independent risk factor in the development of thrombo-embolism [6]. However, at present, the strength and pathophysiology of this association are not fully elucidated.

The objective of this study was to examine the relationship between MPV and unexplained recurrent miscarriage to illuminate the etiopathogenesis of recurrent miscarriage.

Material and methods

The medical records of 274 patients with recurrent miscarriage, who were admitted to the obstetrics clinics of two referral hospitals in Turkey between January 2010 and August 2012, were reviewed. After application of exclusion criteria, 120 patients with unexplained recurrent miscarriage were included in the final analysis, and 154 were excluded from the study. We retrospectively investigated the data of 120 patients with unexplained recurrent miscarriage (group 1), and compared them with the data of 120 match-paired patients in the control group (group 2). The matched factors were age and body mass index (BMI). The study protocol was approved by the Ethics Committee of the Ataturk University Medical Faculty.

We planned our study by adopting the criteria of the American Society for Reproductive Medicine for recurrent miscarriage, which defines it as failure of two or more pregnancies that are confirmed by ultrasound or histopathologic examination. Women of the same age range as group 1, between 22 and 37 years old, with no history of miscarriage or pregnancy loss, who had at least one live birth, were chosen as the control group.

Age and body mass index parameters of the patients were recorded. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Total blood count parameters, including hemoglobin (Hgb), mean corpuscular volume (MCV), red cell distribution width (RDW), white blood cells (WBC), platelets (Plt), and mean platelet volume (MPV), were measured in both groups.

Although MPV and platelet number are well known to remain unchanged during normal pregnancy [7], in order to exclude possible factors affecting those parameters in patients with recurrent miscarriage, blood samples of all women included in the study were taken in a non-pregnant state and at least 3 months after termination of their last pregnancy.

All patients with recurrent miscarriage were evaluated with diagnostic tests for the etiology of recurrent miscarriage, namely uterine cavity evaluation, parental karyotype, TSH, and antiphospholipid antibody (APA) and thrombophilia testing. We classified the patients as having unexplained recurrent miscarriage if their evaluation was negative. Women with recurrent miscarriage who did not have a complete evaluation for underlying causes or who had positive results in routine evaluation were excluded. Patients who had diabetes mellitus, total serum low-density lipoprotein greater than 160 mg/dl, body mass index greater than 30 kg/m^2, arterial hypertension, and who smoked were excluded from the study. These variables may increase MPV.

Uterine cavity evaluation was performed by hysterosalpingography. Thrombophilia testing included proteins C and S, anticardiolipin antibodies, lupus anticoagulant, prothrombin gene, antithrombin III, factor V Leiden, and methylenetetrahydrofolate reductase (MTHFR).

All laboratory tests were performed immediately after sampling. Total blood count parameters, including Hgb, MCV, RDW, WBC, Plt, and MPV, were measured in both groups with an Auto Analyzer (Technicon H.3; Bayer AG, Leverkusen, Germany).

Statistical analysis

Statistical data were analyzed with SPSS 20.0 software and given as mean and standard deviation. Distribution of normality was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney *U* test was used to compare the data pertaining to the study and the control groups. The level of statistical significance was set at $p < 0.05$.

Results

One hundred and twenty women for each group were included in the study. All patients were between 22 and 37 years of age. The average patient age at the time of examination was 29.07 ±2.81 years in group I and 28.53 ±3.5 years in group II ($p > 0.05$). Mean BMI was similar between group 1 and group 2: 22.54 ±3.17 and 22.99 ±2.38, respectively ($p > 0.05$).

Although mean WBC, Hgb, MCV, RDW, and Plt levels were similar in both groups ($p > 0.05$), mean MPV levels were significantly higher in group I (9.45 ±1.09 fl) than in group II (7.63 ±0.52 fl) ($p < 0.001$) (Table I). The comparison of mean MPV values of patients between the groups is shown in Figure 1.

The average number of miscarriages in group 1 was 2.92 ±0.83.

Discussion

Miscarriage, which is the most common complication of the first trimester, is defined as spontaneous loss of a pregnancy before 20 weeks' gestation according to the World Health Organization and before 24 weeks' gestation according to the

Table I. Serum total blood count parameters of the 2 groups

Total blood count parameters	Group 1 (n = 120)	Group 2 (n = 120)	Value of p
Age, mean ± SD [years]	29.07 ±2.81	28.53 ±3.5	0.169
WBC [10^3/µl]	6.90 ±1.23	6.79 ±1.28	0.386
Hgb [g/dl]	12.87 ±1.35	13.02 ±1.37	0.551
MCV [fl]	88 ±6.52	85.86 ±12.66	0.994
RDW (%)	13.81 ±1.41	14.01 ±1.66	0.203
Plt [10^3/µl]	238.93 ±63.88	247.32 ±48.59	0.410
MPV [fl]	9.45 ±1.09	7.63 ±0.52	< 0.001*

**Statistically significant.*

Royal College of Obstetricians and Gynecologists. About 15% of all clinically recognized pregnancies result in miscarriage [8, 9].

The definition of recurrent miscarriage is controversial. The European Society for Human Reproduction and Embryology defines recurrent miscarriage as three or more consecutive pregnancy losses occurring before 20 weeks [10]. Meanwhile, the American Society for Reproductive Medicine defines recurrent miscarriage as two or more failed clinical pregnancies that are documented by ultrasonography or histopathologic examination [2]. Most of the diagnostic tests for evaluation of recurrent miscarriage are expensive and time consuming, raising the question about when testing is warranted. Some clinicians recommend testing after two consecutive losses, while others recommend waiting until three losses.

Recently, a large, single-center, retrospective study on 1020 women with recurrent pregnancy losses aimed to determine whether abnormal test results for factors that are definite or probable causes of recurrent miscarriage occur with equal frequency in women with only two pregnancy losses versus those who have had greater numbers of losses [11]. The study showed no significant difference in the prevalence of abnormal diagnostic test results among women with two versus three recurrent miscarriages and concluded by recommending the evaluation of all couples with two or more consecutive recurrent miscarriages. Although the abovementioned study included patients with biochemical pregnancies, which comprises a considerable increase in the patient population with recurrent miscarriage, it appears reasonable to start the investigations after two or more consecutive spontaneous miscarriages to determine the cause of the pregnancy loss. In our study, to avoid any bias by considering biochemical pregnancies in the diagnosis of recurrent miscarriage, we included only patients with two or more miscarriages of clinically documented pregnancies (documented by ultrasound or histopathologic examination), as proposed by the

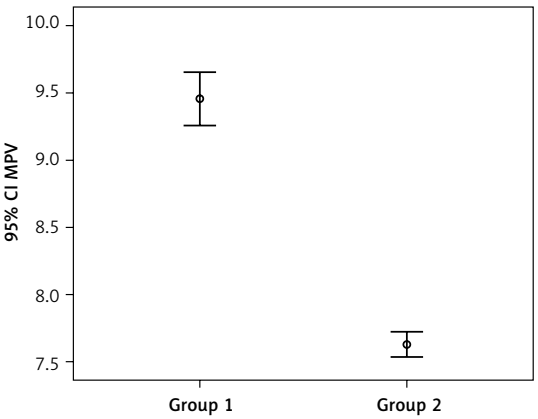

Figure 1. Comparison of mean MPV values of patients between group 1 and group 2

American Society for Reproductive Medicine [2]. The average number of miscarriages in group 1 was 2.92 ±0.83.

Recurrent miscarriage affects 1% of couples trying to conceive [12]. Unfortunately, the etiology of recurrent miscarriage cannot be explained in 50% of cases [2]. There are many well-established risk factors for recurrent miscarriage [13].

The term thrombophilia is used to describe a disorder associated with an increased tendency to venous thromboembolism [14]. Thrombophilia is also associated with an increased risk of both single miscarriage and recurrent miscarriage [15]. Various forms of thrombophilia are associated with recurrent miscarriage, but the causal relationship is not yet fully illuminated. However, micro-emboli in the uteroplacental circulation, which lead to placental insufficiency and inflammation, are thought to cause recurrent miscarriage, placental abruption, preeclampsia and intrauterine growth retardation in pregnant women with thrombophilia [16].

The most important thrombophilia associated with recurrent miscarriage is antiphospholipid syndrome (APS) [12]. Antiphospholipid antibodies have been associated with a variety of medical problems, including arterial and venous thrombosis, recurrent miscarriage, and severe pregnancy

with early onset, intrauterine growth retardation and fetal loss. Antiphospholipid antibodies used in the diagnosis are lupus anticoagulant, anticardiolipin antibodies, and anti-β_2-glycoprotein I [17]. Antiphospholipid syndrome is a treatable cause of recurrent miscarriage. The standard treatment for APS is low-dose aspirin and heparin. While live birth rates in untreated patients were about 10%, it was reported as 71% in treated patients [18].

Factor V Leiden is a common mutation (5% in whites) [19]. While there are studies claiming that factor V Leiden mutation and prothrombin G20210A gene mutation increase recurrent miscarriage rates [14], there are publications suggesting that they constitute no such difference [20]. Antithrombin 3 deficiency is the first thrombophilia defined. Initial research established an increased risk of miscarriage in women with antithrombin 3 deficiency [21]; however, subsequent publications have challenged this [22]. A recent meta-analysis demonstrated that protein S deficiency and protein C deficiency are not associated with recurrent miscarriage [15].

Mean platelet volume correlates with platelet function and activation, whether measured as aggregation, thromboxane synthesis, β-thromboglobulin release, procoagulant function, or adhesion molecule expression [23]. Since increased MPV levels are generally considered as a vascular risk factor, the results of our study suggested the role of platelet activation in the vascular pathogenesis of recurrent miscarriage.

Increased MPV has been defined as an independent risk factor in the development of thromboembolism [6]. Mean platelet volume increase has been associated clinically with cardiovascular and cerebrovascular morbidity [24, 25]. Increased MPV has also been identified as an independent risk factor for myocardial infarction in patients with coronary heart disease [6]. In addition, MPV was found to be increased in some conditions with increased risk of cardiovascular morbidity, including diabetes mellitus [26], hypercholesterolemia [27], obesity, hypertension, and smoking [28]. By excluding patients with conditions that are known to increase MPV, namely diabetes mellitus, hypercholesterolemia, obesity, hypertension, and smoking, we focused on explaining the association between MPV and recurrent miscarriage independently.

Boriboonhirunsarn *et al.* [29] suggested that high values in MPV are useful in differentiating severe pre-eclamptic cases from normal pregnancy. Jaremo *et al.* [30] declared that pre-eclamptic cases involve lower platelet numbers and higher MPV values.

In our review of the literature, we found no publications studying the association between MPV and recurrent miscarriage. To our knowledge, this study is the first to investigate the association between MPV and recurrent miscarriage.

This study detected significantly higher MPV values in patients with recurrent miscarriage. Our results support the thesis that increased MPV leads to thrombosis, which in turn leads to micro-emboli in the uteroplacental circulation, placental inflammation and insufficiency and consequently recurrent miscarriage. Although MPV seems a simple and cost-effective method, there are insufficient data supporting its ability to predict the risk of thromboembolic events in recurrent miscarriage.

The retrospective nature and the small number of subjects can be regarded as the main limitations of this study.

In conclusion, In our study, MPV values in women with recurrent miscarriage were significantly higher than in the control group. Higher MPV values in the study group suggest and support the importance of thromboembolic events in the etiology of recurrent miscarriage. Measurement of MPV as a simple method for prediction of recurrent miscarriages in patients who have had one miscarriage may have practical value and needs further evaluation.

Conflict of interest

The authors declare no conflict of interest. We declare that there are no financial grants, other funding or industrial affiliations associated either with this study or the authors.

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