

RESEARCH ARTICLE

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Is There Any Relation Between Recurrent Miscarriage and Complete Blood Count Values? A Case-Control Study

ABSTRACT

Objective: It was aimed to examine the relationship of complete blood count values with recurrent miscarriage.

Methods: We carried out a case-control study of patients who had recurrent miscarriage between 2010-2018. Data were collected from 50 patients who were meeting the case group inclusion criteria, and age-matched healthy control group with at least one live birth who consisted of 60 women. Red blood cell (RBC), hemoglobin (HB), hematocrit (HTC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), red cell distribution width (RDW) and plateletcrit count (PCT) were examined by complete blood count. SPSS 20.0.0 software was used for statistical analysis. P values <0.05 were regarded as statistically significant.

Results: The mean age of the case group was 29.8±5.8 years, and the mean age of the control group was 28.7±5.2 years (p>0,05). MPV and RDW values and PCT calculations were significantly higher than healthy control group (p<0.05). MCHC levels of case group were lower than control group (p<0.05). There were no significant differences between the case and control groups in terms of RBC, HB, HCT, MCV, MCH, PLT, and PDW (p>0.05).

Conclusions: Complete blood count parameters such as high MPV, RDW, PCT, and low MCHC could be considered as an important predictor of recurrent miscarriage. Our findings should be supported by further prospective studies involving a larger number of patients in order to clarify the relationship between these blood cell function markers and recurrent miscarriage.

Keywords: Mean Platelet Volume, Recurrent Miscarriage, Complete Blood Count

Tekrarlayan Düşük Ve Tam Kan Sayımı Değerleri Arasında Herhangi Bir İlişki Var Mı? Bir Vaka-Kontrol Çalışması

ÖZET

Amaç: Tam kan sayımı değerleri ile tekrarlayan düşük arasındaki ilişkinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: 2010-2018 yılları arasında tekrarlayan düşük yapan hastalarda vaka-kontrol çalışması yaptık. Vaka grubunda dahil edilme kriterlerini karşılayan 50 hastanın verilerini, 60 kadından oluşan, en az bir canlı doğum yapmış aynı yaş grubundan kontrol grubu ile eşleştirdik. Tam kan sayımında kırmızı kan hücresi (RBC), hemoglobin (HB), hematokrit (HTC), ortalama korpüsküler hacim (MCV), ortalama korpüsküler hemoglobin (MCH), ortalama korpüsküler hemoglobin konsantrasyonu (MCHC), trombosit sayısı (PLT), trombosit dağılım genişliği (PDW), kan sayımında ortalama trombosit hacmi (MPV), kırmızı hücre dağılım genişliği (RDW) ve plateletkrit hesaplaması (PCT) incelendi. İstatistiksel analiz için SPSS 20.0.0 yazılımı kullanıldı. P<0,05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Kontrol grubunun yaş ortalaması 28,7±5,2 yıl iken; vaka grubunun 29,8±5,8 yılı (p>0,05). Vaka grubunda MPV ve RDW değerleri ile PCT hesaplaması sağlıklı kontrol grubundan anlamlı olarak yüksek bulundu (p<0,05). Vaka grubunun MCHC düzeyleri kontrol grubundan düşüktü (p<0,05). Vaka ve kontrol grubu arasında RBC, HB, HCT, MCV, MCH, PLT ve PDW açısından anlamlı bir fark yoktu (p>0,05).

Sonuç: Yüksek MPV, RDW, PCT ve düşük MCHC gibi tam kan sayımı parametreleri, tekrarlayan düşüklerin önemli bir belirleyicisi olarak düşünülebilir. Bulgularımız, bu kan hücresi fonksiyon belirteçleri ve tekrarlayan düşükler arasındaki ilişkiyi netleştirmek için daha fazla sayıda hasta içeren ileriye dönük çalışmalar ile desteklenmelidir.

Anahtar Kelimeler: Ortalama Trombosit Hacmi, Tekrarlayan Düşük, Tam Kan Sayımı

INTRODUCTION

Recurrent miscarriage are defined as three or more consecutive fetal losses prior to 20 weeks gestation or with low birth weight less than 500 gram (1). This is a traumatic process that inflicts emotional and physical damage on families. Recurrent miscarriage is encountered in approximately 1% of fertile women. Various causes of recurrent miscarriage are known, including genetic, endocrinological, infectious, anatomical, and immunological causes (2). However, the etiology of approximately 50% of cases is uncertain (3). It is of great important in that context for physicians to accurately identify and manage patients presenting with recurrent pregnancy loss.

The hematological system plays an important role in the completion of implantation and placental development. Implantation of the fertilized egg into the decidual layer of the uterus depends on connective compatibility between the fetus, placenta and maternal circulation. Various changes resulting in a disposition to thrombus during pregnancy can leads to pregnancy losses by affecting the implantation stage (4).

Platelets and other complete blood count parameters play an important role in the pathology of vascular diseases (5). Previous studies support the idea that variability in platelet count, mean platelet volume, platelet distribution width, hemoglobin, hematocrit, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, reticulocyte count, and reticulocyte distribution width can lay the foundation for recurrent pregnancy losses by affecting the homeostasis of the hematological system (6, 7).

The complete blood count test is accessible and inexpensive, and the determination of parameters associated with recurrent pregnancy losses may be indicative before detailed tests are performed (8). The purpose of this study was to investigate whether any difference in complete blood count values would be observed between patients with recurrent pregnancy losses and women with children and no history of miscarriage.

MATERIAL AND METHODS

This research was conducted as a case-control study. The study data were obtained retrospectively from hospital records. The case group consisted of patients presenting to the Atatürk University Medical Faculty Medical Genetics Outpatients Department, Turkey, due to recurrent miscarriage in 2010-2018. We accessed the clinical data for 220 patients suitable for evaluation as the case group. The control group consisted of healthy women from a similar age group with at least one pregnancy.

Inclusion criteria for the case group were:

- Age 18-40 years,
- History of at least three consecutive recurrent pregnancy losses,

- Pregnancy losses occurring before the 20th week of gestation,

- At least 12 weeks having passed since miscarriage in order to exclude factors likely to affect blood count values, and no new pregnancy having occurred during that time,

- No systemic-autoimmune disease,
- Absence of any health problem representing an obstacle to the study, and
- Patients not using non-steroidal anti-inflammatory drugs, oral contraceptives, hormonal therapy, anti-platelet or anti-coagulant drugs capable of affecting platelet functions at time of blood collection.

Exclusion criteria in the case group were:

- Recurrent miscarriage outside the 18-40 age range,
- Pregnancy losses occurring after 20 weeks of gestation, and
- Drug use or systemic or autoimmune disease capable of affecting blood count values.

Data were collected for 50 patients meeting the case group inclusion criteria. Sixty fertile women at least one live birth were enrolled in the control group. Patients presenting to the Atatürk University Medical Faculty Family Medicine Outpatients Department and meeting the relevant inclusion criteria were included in the control group.

Inclusion criteria for the control group were:

- Age 18-40,
- History of at least one live birth,
- At least 12 weeks having elapsed since the latest birth,
- No previous pregnancy loss,
- No systemic-autoimmune disease,
- No other health problem capable of constituting an obstacle to the study, and
- Not using non-steroidal anti-inflammatory drugs, oral contraceptives, hormonal therapy, anti-platelet or anti-coagulant drugs capable of affecting platelet functions at time of blood collection.

Age and blood count values were examined for women meeting the case and control group inclusion criteria. Red blood cell (RBC), hemoglobin (HB), hematocrit (HTC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), and red cell distribution width (RDW) were examined at complete blood count. In addition, plateletcrit (PCT) values showing the percentage of blood made up of platelets were calculated using the formula $MPV (fL) = [(plateletcrit (\%)/platelet count (\times 10^9/l)] \times 10^5$ (9).

Approval for this study was granted by the Atatürk University Medical Faculty Clinical

Research ethical committee (No. B.30.2.ATA.0.01.00/31 dated 08.12.2016).

SPSS 20.0.0 software was used for statistical analysis. Descriptive statistics were expressed as number and percentage for categorical data and mean and standard deviation for numerical data. Compatibility with normal distribution of numerical variables was examined using skewness. Student's T test was to compare mean individual blood count parameters between the case and control groups. Odds ratios were calculated for parameters in which differences were identified, and were presented together with the confidence interval. *p* values <0.05 were regarded as statistically significant.

RESULTS

One hundred ten individuals were included in this retrospective study, 50 in the case group and 60 in the control group. The mean age of the case group was 29.8±5.8 years, and the mean age of the control group was 28.7±5.2 years (*p*=0.20).

A comparison of blood count parameters in the case and control groups is shown in Table 1. MPV, RDW and MCHC values and PCT calculations were significantly higher on the case group than in the control group (*p*<0.05). No significant difference was determined between the groups in terms of HB, HCT, PLT, PDW, RBC, MCV, or MCH values (*p*>0.05).

Table 1. Comparison of blood count parameters in the case and control groups

Blood count parameters	Case group n=50	Control group n=60	<i>p</i> value
RBC (x10 ¹² /L)	4.7±0.4	4.8±0.3	0.935
HB (g/dl)	13.1±1.7	13.6±1.1	0.070
HCT (%)	40.8±4.3	41±3.1	0.888
MCV(femtoliters)	85.1±7.2	85.3±5.4	0.808
MCH (pg/cell)	27.8±2.7	28.4±1.9	0.250
MCHC (mg/dl)	32.4±1.6	33.3±0.9	0.001
PLT (x10 ⁹ /L)	279.18±61.6	270.80±62.8	0.480
PDW (%)	15.7±1.8	14.9±2.5	0.056
MPV (µm ³)	9.8±1.7	8.3±1.8	0.000
PCT (%)	0.27±0.74	0.22±0.65	0.001
RDW (%)	14.5±2.6	13.6±1.3	0.014

Since MPV elevation was significantly greater in the case group than in the control group, the odds ratio was calculated using cross tabulation (Table 2). Accordingly, 72.2% of MPV elevation was seen in the case group and 27.8% in the control group (O.R=0.25 (0.08-0.78] 95% confidence interval [CI]).

Table 2. Case and control group distribution of MPV levels

	Case Group n=50	Control Group n=60
Normal MPV[n(%)]	37(40.2%)	55(59.8%)
High MPV [n(%)]	13(72.2%)	5(27.8%)

O.R=0.25 [0.08-0.78, 95% CI]

RDW elevation was also significantly greater in the case group compared to the control group, and odds ratios were again calculated using cross tabulation (Table 3). Accordingly, RDW elevation was determined in 52.9% of the case group and 47.1 of the control group (O.R=0.7 [0.24-1.97], 95% CI).

Table 3. Distribution of RDW levels in the case and control groups

	Case Group n=50	Control Group n=60
Normal RDW [n(%)]	41(44.1%)	52(55.9%)
High RDW [n(%)]	9(52.9%)	8(47.1%)

O.R=0.7 [(0.24-1.97), 95% CI]

DISCUSSION

Recurrent miscarriages represent 1% of all pregnancies, and are an important reproductive health problem. The etiology is unknown in approximately half of recurrent pregnancy losses (10). Some recent research has referred to novel biomarkers in pregnancy-related complications, particularly blood count parameters (11). Retrospective examination of blood count specimens from women with recurrent miscarriage in our study revealed higher MPV, RDW, PCT calculations and lower MCHC values and compared to the healthy control group.

The complete blood count is a simple, easily available, and economic test involving such parameters as WBC, RBC, HB, HCT, MCV, MCH, MCHC, RDW, PLT, MPV, and PDW. Studies have shown an association between some blood count values and various clinical conditions. Several previous studies have examined the relation between chronic diseases, cancers and infections and platelet parameters at complete blood count (12-14). Variable MPV values in particular are thought to be related to vascular, autoimmune and thrombophilic diseases. The effect of MPV and PLT values has particularly been investigated in terms of vascular thromboses. Platelets' prothrombotic potential exhibits positive correlation with platelet dimensions. An increased platelet volume is a probable indication of platelet activity. Platelet indices have been investigated in prothrombotic diseases, and findings showed that high MPV levels reflect platelet activation and enlargement (15). A lower platelet count and higher MPV have been observed in women with pre-eclampsia compared to normal gravidas (16). Studies show that platelet parameters are in terms of risk of vascular thrombosis and of both arterial and venous thrombosis.

Pregnancy is a state of hypercoagulation in which the concentrations of coagulation factors change. Platelet activity is also reported to increase during pregnancy (17). This prothrombotic state has been reported to be capable of concluding with an exaggerated hemostatic response and to be capable

of leading to utero-placental vascular thrombosis, followed by fetal loss (18). One study investigating the relation between pregnancy and hematological parameters showed that PLT values increased with weeks of gestation, and also that MPV values were higher those than in non-pregnant subjects (19). This accounts for the tendency to thromboembolism and state of hypercoagulation experienced in pregnancy. Inability to tolerate this state of hypercoagulation seen in pregnancy can result in pregnancy losses (5). Similarly, in the present study, the higher MPV values in subjects with recurrent pregnancy losses compared to the healthy control group supports this finding from the literature.

Several cytokines are released during embryo implantation, placenta formation and angiogenesis in pregnancy. These cytokines play an active role in the inflammation process that causes tissue damage or repair through complement activation and apoptosis. The inflammatory cytokines TNF- α and INF- γ have been shown to play an important role in spontaneous abortion (2). The correlation between high MPV as an inflammatory marker and activation of symptoms in inflammatory disease has been demonstrated before researches (20). The higher MPV value is shown to be associated with inflammation; in subjects with recurrent miscarriage in our study support this finding.

To our best knowledge, there is no research about the relationship with MCHC and recurrent miscarriage. However, MCHC has been proved an independent prognostic factor of acute myocardial infarction. Low MCHC level were significantly associated with hospital mortality among patients with acute myocardial infarction (21). According to our results, low MCHC level is associated with recurrent pregnancy loss. Further investigations are need to evaluate the relation between low MCHC level and recurrent pregnancy loss.

RDW is an indicator of variation and heterogeneity of red cells and it is generally used for anemia classification. Increased RDW values have often been associated with anemia (22). Besides, this parameter has been shown to be associated with some clinical features such as waist circumference, body mass index, high alcohol

consumption, blood pressure, diabetes mellitus, and low degree of inflammation. Women with a history of recurrent pregnancy loss had higher RDW values than the healthy control group in a previous study (23). Similarly, RDW values were significantly higher in the case group than control group in our study. The relation may be associated with to have anemia or low degree inflammation. Further investigations are needed to explain correlation of RDW values and recurrent miscarriage.

Platelet function disorders must be investigated if the etiological factor in recurrent pregnancy losses cannot be identified. This is because the cause of utero-placental thrombosis may be associated with platelets. One previous study reported higher PDW values in women with recurrent pregnancy losses of unknown cause compared to a control group. That study also showed that increased PDW values might be more significant than MPV values in terms of indicating miscarriage (24). Studies have shown that accompanying PDW elevation is more valuable than MPV elevation alone in subjects with a disposition to thromboembolic events (25). Conversely, we determined no difference in terms of PDW values between women with recurrent miscarriage and healthy controls. Platelet indices calculated from the platelet count include also PCT. PCT has been determined as a potentially useful marker for thromboembolic disease such as pre-eclampsia and eclampsia instead of platelet count alone (26). We observed the high level of PCT in case group. Further studies are needed to investigate the importance of PDW and other platelet function markers in the etiology in patients with a history of recurrent miscarriage.

There are some limitations of this study. First was to collect data with retrospective method. This was restricted to collect some data that can influence the results. On the other hand, we compared the results with a healthy control group. There is limited investigation the relationship between complete blood count parameters and recurrent miscarriage. Further prospective trials are required in this field.

Conflicts of Interest

The authors have no financial conflicts of interest.

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