European Journal of Therapeutics

DOI: 10.5152/EurJTher.2017.227

Original Research / Özgün Araştırma

The Efficacy of Haematologic Parameters in the Diagnosis of Missed Abortus

Hematolojik Parametrelerin Missed Abortus Tanısına Etkileri

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ABSTRACT

Objective: The aim of the present study was to investigate the efficacy of hematologic parameters in diagnosing missed abortus (MA). Our second aim was to elucidate the diagnostic value of maternal serum cancer antigen 125 (CA 125) levels in missed abortion.

Methods: Hemoglobin, white blood cell, neutrophil, lymphocyte, and platelet levels; mean corpuscular volume; mean platelet volume (MPV); and red cell distribution width (RDW) in complete blood count samples were obtained from all patients diagnosed with MA (group 1; n=90) and from women with healthy pregnancies (group 2; n=143).

Results: Lymphocyte, platelet, and RDW variables were significantly higher in group 1 (p=0.03, p=0.003, and p=0.005, respectively). High RDW value was independent predictors of MA (OR: 0.810, p<0.05). Mean CA 125 levels between the groups were similar. There was no significant difference in other hematologic laboratory parameters between the groups.

Conclusion: Of all hematologic inflammatory markers, higher RDW value was the only marker associated with MA. RDW might be used as an early promising predictor of MA with low cost. Second, we found that CA 125 and other hematologic inflammatory markers, such as MPV and neutrophil/lymphocyte ratio, are not good markers for predicting MA.

Keywords: Cancer antigen 125, hematologic parameters, missed abortus, red cell distribution width

ÖZ

Amaç: Missed Abortus (MA) kapalı bir serviksle maternal-fetal yapılara ait ölü dokuların günler, haftalar hatta aylarca uterin kavite içinde kalmasıdır. Fetal ölüm ve abortusun tanısı temelde klinik ve ultrason yardımı ile konulur. Gelişmiş ultrason görüntü teknikleri sonrasında MA daha sık görülmeye başlamıştır. Sağlıklı bir gebeliğin devamı ya da tespiti hakkında henüz güvenilir bir biyokimyasal marker yoktur ve etyolojisi hala net değildir. Yeni çıkan çalışmalarda bazı hematolojik parametreler ile tekrarlayan gebelik kayıpları arasında ilişki bulunmuştur. Bu çalışmada amacımız hematolojik parametrelerin MA tanısına etkisini araştırmaktır. İkincil amacımız serum Ca 125 düzeylerinin missed abortus tanısındaki rolünü değerlendirmektir.

Yöntemler: Bu çalışmaya 90'nı missed abortus, 143'ü sağlıklı kontrol olmak üzere toplamda 233 gebe dahil edilmiştir. Bu hastaların rutin hematolojik parametrelerindeki hemoglobin, beyaz küre, nötrofil, lenfosit, ortalama korpuskular hacim (MCV), ortalama platelet hacmi (MPV), eritrosit dağılım genişliği (RDW) değerleri kaydedilmiştir. Ayrıca tüm hastaların serum Ca 125 değeri de bakılıp not edilmiştir.

Bulgular: MA grubunda lenfosit, platelet ve RDW anlamlı olarak yüksek bulunmuştur. (sırasıyla; p=0,03, p=0,003, p=0,005) Gruplar arasında anlamlı çıkan bu değerler multivaryant analizde tekrar bakıldığında MA tanısında RDW'nin bağımsız faktör olduğu görülmüştür (OR: 0,810, p<0,05). Gruplar arasında Ca 125 değerleri benzer bulunmuştur (p=0,7). Gruplar arasında diğer hematolojik parametreler açısından anlamlı fark saptanamamıştır.

Sonuç: Bakılan tüm hematolojik parametreler arasında yüksek RDW missed abortusların tanısıyla ilişkili bulunmuştur. Düşük maliyetli rutin kullanılan bu testler erken tanıda ümit vaat etmektedir.

Anahtar kelimeler: Eritrosit dağılım hacmi, hematolojik parametreler, kanser antijen 125, missed abortus

This study has been presented as a verbal statement in the 14th National Gynecology and Obstetric Congress, 5–9 October 2016, Antalya, Turkey.

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Received/Geliş Tarihi: 01.12.2017 • **Accepted/Kabul Tarihi:** 05.12.2017

INTRODUCTION

Missed abortus (MA) is the term that is used to describe dead products of conception retaining for days, weeks, or even months in the uterus with a closed cervical os (1). With the development of ultrasound image techniques, the incidence of MA has become higher (3.89%-14.1%) (2). Risk factors for MA are parental chromosomal abnormalities, hereditary thrombophilia, endocrinological disorders, immunological factors, infections, apoptosis, oxidative stress, and environmental factors (3). However, the exact cause of missed abortion remains unknown.

In recent years, the role of hematologic inflammatory markers, such as neutrophil/lymphocyte ratio (NLR), red cell distribution width (RDW), and mean platelet volume (MPV) has attracted attention in recurrent pregnancy loss (4, 5).

Red cell distribution width is one of the routinely available components of total blood count tests and it is the measure of variability in the size or volume of red blood cells (4). When different red cell sizes are observed (anisocytosis) in the peripheral blood smear, RDW values are elevated and this elevation is said to be associated with recurrent pregnancy loss (4, 5). It is concluded that RDW is a low-cost, routine marker for predicting recurrent pregnancy loss in patients with a history of at least one abortus (4, 5). Moreover, it is a reliable and promising independent marker for severe pre-eclampsia (6) and is an easily available marker with no additional costs in cardiovascular risk even in young patients (7).

Cancer antigen 125 (CA 125) is a basic known marker for predicting epithelial ovarian cancer, and it is shown that CA 125 can be expressed in the fetus and on serous surfaces, such as the pericardium, pleura, and peritoneum (8). It can also be histochemically detected in the epithelium of the endocervix and endometrium. In addition, increased CA 125 levels can be found in healthy pregnant and non-pregnant women (8).

Higher CA 125 levels are detected in patients with vaginal bleeding irrespective of them having a viable pregnancy or a gestational sac at a normal location (9). On the other hand, in another study, decreased CA 125 levels were observed in a similar group of patients with vaginal bleeding (10). Therefore, the role of CA 125 in abortions and pregnancy is still controversial, and studies involving larger numbers of participants should be conducted.

Ultrasonography is mainly used for diagnosing fetal demise and abortion. There is no reliable biochemical marker for detecting a viable pregnancy or defining a biomarker for pregnancy outcome.

There is no research conducted on hematologic parameters associated with MA. We have concentrated on this issue. Therefore, in our study, we investigated the efficacy of hematologic inflammatory markers and maternal serum CA 125 levels in diagnosing MA.

METHODS

A total of 90 patients (group 1) with missed abortion between April and December 2014 were included in our study. Transvaginal ultrasound was performed in all cases, and the diagnosis was confirmed by repeated ultrasound. We used ultrasound findings and the date of the last menstrual period to determine the gestational age. An intact gestational sac without fetal cardiac activity during 6 weeks and an intrauterine gestational sac with a diameter of >10 mm but without a yolk sac were defined as first trimester missed abortion (1). Fetal demise that occurs before several weeks along with absent uterine activity to throw out the product of conception without any vaginal bleeding is usually described as a second trimester missed abortion (1). The control group (group 2) included 143 pregnant women with viable and healthy intrauterine fetus. We confirmed the gestational age and fetal cardiac activity using ultrasound. Both groups had a gestational age range of pregnancies between 6 and 16 weeks. Multiple pregnancies and pregnancies with structural fetal anomalies were excluded. Furthermore, patients with anemia, hemoglobinopathy, any systemic or chronic disease, a history of bleeding or coagulation disorder, or anticoagulant therapy were excluded. All patients were ultrasonographically examined for uterine abnormalities. We evaluated antibodies for infection, such as *Toxoplasma gondii*, rubella, cytomegalovirus, and herpes simplex virus (TORCH) and anticardiolipin and antinuclear antibodies in all patients. Our study was conducted according to the recommendations of the Declaration of Helsinki on biomedical research involving human subjects. A written informed consent was obtained from each participant.

In all cases, we collected blood samples in tripotassium Ethylene diamine tetra acetic acid (EDTA) tubes when MA was diagnosed before taking any medication. All measurements of hematologic parameters were performed using the Beckman Coulter automated blood count analyzer (Beckman Coulter Inc., CA, USA) 30 min after blood collection. CA 125 levels were determined by the electrochemiluminescence immunoassay method using the DXI 800 automatic quantitative hematology analyzer (Beckman Coulter Inc., CA, USA).

Statistical Analysis

We performed all analyses using SPSS (Statistical Package for Sociel Sciences) Version 18.0 (IBM Corp.; Armonk, NY, USA). We expressed quantitative variables as mean±standard deviation for parametric variables. We used median values as non-parametric variables and determined minimum-maximum levels. We analyzed continuous variables for normal distribution with the Kolmogorov-Smirnov test. A value of $p<0.05$ was considered to be significant. We determined differences in continuous variables between the two groups using the Student's t-test or Mann-Whitney U test. Significant parameters ($p<0.05$) were used in the multivariate analysis. We performed logistic regression analysis for multivariate analysis of independent predictors.

RESULTS

We examined a total of 233 patients, including 90 patients with MA as group 1 and 143 healthy pregnant patients as group 2. The main characteristics of the groups and mean values of hematologic laboratory parameters for each group are presented in Tables 1 and 2, respectively.

Tablo 1. General baseline characteristics of the groups

	Missed abortus (N=90)	Control group (N=143)	p
Age	27.2±6.7	26.7±5.7	0.5
BMI	24±3	24±4	0.8
Gravidity	2.7±1.5	2.5±1.3	0.2
Parity	2.0±0.9	1.8±1.3	0.2
Gestational age (week)	9.6±1.9	9.3±2.4	0.3

Data are presented as mean±SD
BMI: body mass index

Tablo 2. Investigation of hematologic laboratory parameters between the groups

	Missed abortus (N=90)	Control group (N=143)	p
Hemoglobin (g/dL)	12.9±1.0	12.8±1.1	0.2
WBC ($\times 10^3$/μL)	8.6±2.5	8.3±2.0	0.3
Neutrophil ($\times 10^3$/μL)	5.9±2.1	5.7±1.8	0.5
Lymphocyte ($\times 10^3$/μL)	2.1±0.6	1.9±0.4	0.03
Platelet ($\times 10^3$/μL)	253±73	229±46	0.003
MCV (fL)	84±6	85±7	0.9
MPV (fL)	8.8±1.3	8.8±0.9	0.9
RDW (%)	13.4±2.0	12.8±1.3	0.005
CA 125	37.2±23.4	38.1±19.7	0.7
TSH	1.4±0.7	1.3±0.8	0.4
Glucose	90±11	89±15	0.8
NLR	2.8±1.1	2.9±1.1	0.4
PLR	124±52	120±34	0.4

Data are presented as mean±SD.

WBC: white blood cell; MCV: mean corpuscular volume; MPV: mean platelet volume; RDW: red cell distribution width; CA 125: cancer antigen 125; TSH: thyroid stimulating hormone; NLR: neutrophil/lymphocyte ratio; PLR: platelet/ lymphocyte ratio

Mean values of age, gravidity, parity, and gestational age were similar in both groups. As shown in Table 2, the lymphocyte, platelet, and RDW values were significantly higher in group 1. The mean values of CA 125 between the groups were similar. There was no significant difference in other hematologic inflammatory markers between groups. Variables found to be statistically significant in univariate analysis between our groups were entered into multivariate analysis. Only RDW values were significantly higher in group 1. High RDW value was an independent predictor of MA (OR: 0.810, $p<0.05$).

DISCUSSION

To the best of our knowledge, this is the first case-control study to investigate the efficacy of hematologic inflammatory markers in diagnosing MA. Moreover, our study is one of the studies with a large number of cases of MA. The major finding of our study is that RDW might be used as an early marker of MA.

The etiology of MA remains unclear. In the literature, adenosine deaminase activity (ADA) (11), stress factors [serum cortisol and interleukin (IL)-12] (12), heparin-binding epidermal growth factor (HB-EGF) (13), leptin levels (14), and inflammatory cytokines (15) in maternal serum and placenta are assessed in MA. Based on these data series, low ADA, higher cortisol levels, lower IL-12 levels, increased HB-EGF expression, and lower tumor necrosis factor alpha in early pregnancy may play a role and lead to loss of pregnancy.

Early pregnancy is in a hypoxic situation that may quicken angiogenesis. Moreover, in a recent study, it has been reported that severe hypoxia and aberrant vascular endothelial growth factor signaling may cause MA (16). All studied markers are expensive and include non-routine test; in addition, the exact mechanism underlying the relationship with missed abortion are unknown.

MPV, which shows platelet activation and function, is measured in MA. MPV is a precise measure of the platelet size. Larger platelets have higher MPV values; therefore, higher MPV is more reactive and causes higher measures of the prothrombotic factors hemostatically (17). Moreover, in a group of patients with maternal thrombophilia, hypercoagulability may lead to low perfusion of the placenta, and finally, this may cause loss of the fetus (17). In the case of MA, Kosus et al. (18) compared MPV values and platelet counts of 100 patients with MA and 100 healthy controls. Both groups were between 6 and 13 weeks of gestation and had similar demographic characteristics. They found slightly increased MPV values in patients with missed abortion. They concluded that slightly increased MPV might encourage thrombosis (18). On the other hand, in a recent study, investigators suggested that MPV was significantly lower in patients with miscarriage than in the control group (19). The miscarriage group comprised biochemical and clinical abortions. The group with a miscarriage after biochemical pregnancy had the lowest MPV value. They concluded that due to inflammation and bleeding, platelets with higher activity (larger platelets) can migrate to the region in earlier gestational weeks (19). This may lead to a decrease in MPV in maternal circulation. Similarly, MPV decreases during active periods of inflammatory diseases, such as ankylosing spondylitis, systemic lupus erythematosus, and rheumatoid arthritis (20, 21).

In our study, MPV, RDW, and NLR were assessed in 90 patients with MA. These parameters were included in routine blood count measurements and did not require an additional cost. To the best of our knowledge, this was the first study in which RDW, NLR, and MPV were investigated in patients with MA. In our study, among these parameters, only RDW values were significantly different between the groups. Both elevated (18) and lower MPV values (19-21) were associated with inflammation. However, we could not deduce and show this data in our current study. Higher RDW values could be found in circumstances associated with incapability of red cell production, for example, due to B_{12} or folate inadequacy, iron deficiency, and hemoglobinopathies. Furthermore, RDW val-

ues were elevated with destruction of red cells and in hemolysis (22). Recently, Kurt et al. (6) found that RDW values were significantly higher in the severe pre-eclampsia group than in the mild pre-eclampsia group. Their study results revealed that RDW values were associated with existing pre-eclampsia and also indicated its severity (6). However, the accurate mechanism associated with hypertension and RDW has not been determined yet. Elevated inflammation is the most popular theory. It has been reported that in patients with underlying pre-eclamptic placental hypoxia, oxygen). Thus, the more the flow of immature erythrocytes increases in the vessels, the more the RDW value elevates. Dundar et al. (5) retrospectively evaluated 60 patients with recurrent pregnancy loss, 60 healthy pregnant patients in the first trimester, and 60 healthy non-pregnant multipara patients. Finally, they found a significant and positive relationship between RDW and platelet distribution width (PDW) (r=0.615, p=0.001), RDW and plateletcrit level (r=0.343, p=0.007), and PDW and plateletcrit level (r=0.340, p=0.008) in patients with recurrent pregnancy loss. They concluded that elevated PDW and RDW values were associated with recurrent pregnancy loss. They thought that inflammation and thromboembolism resulted with anisocytosis, causing elevation of RDW (5). Moreover, RDW is an available marker for myocardial infarction in young patients, but underlying mechanisms have not been clearly demonstrated (7). In our study, we found high lymphocyte, RDW, and platelet values in the MA group. Hypoxia and inflammation during abnormal pregnancy may lead to this result. In our results, there was no significant difference in MPV and NLR values between groups. Although NLR is a well-studied hematologic parameter and an independent predictor for ovarian torsion and pre-eclampsia, underlying mechanisms of inflammation in missed abortion might be different (21, 23).

RDW for red blood cells, MPV for platelets, and NLR for response to stress-related systematic inflammation are inexpensive daily parameters that are used in routine laboratory test. As mentioned above, several markers are studied to determine the etiology of MA, but it is still unclear and something different whetehr both inflammation and thrombosis might totally play a role via different mechanisms. Further studies with larger series are needed for clarifying and explaining the diagnostic potential of this situation. In addition, every laboratory has a specific normal range, but there are no generally accepted mean values. Moreover, measurements of these tests can be affected by both environmental and laboratory conditions, such as temperature, storage conditions, and time until measurement.

In addition, we measured CA 125 levels in patients with MA. There was no significant difference in CA 125 levels between groups. We have planned to study CA 125 levels both laboratory and histopathologically, but we could only investigate the laboratory part. CA 125 levels in patients with abnormal pregnancy during the first trimester were evaluated in some studies, but there was no significant difference in mean CA 125 levels among the groups (24, 25). Check et al. (26) found a relationship between spontaneous abortion and elevated CA 125 levels, whereas other studies reported no significant difference in serum CA 125 levels (24, 25, 27). We also could not find a statistical difference, similar to the results of the previous studies. Scarpellini et al. (28) found higher CA 125 levels in the group with threatened abortion than in the controls (healthy pregnancy). Moreover, they concluded that damages in the deciduas and the fetal membrane resulted with elevation of maternal serum CA 125 levels.

In our study, preserved membranes in cases of MA may play a role in insignificant CA 125 results. Actually, there are many reasons that alter CA 125 levels in circulation, and the role and mean cut-off levels have not been clarified yet (8). Furthermore, the origin (fetal or decidual) of this CA 125 is still controversial. In a different study, the importance of diagnostic and prognostic values of repeated maternal CA 125 levels in early pregnancy was emphasized (29). They measured serum CA 125 levels of symptomatic pregnant patients with failed diagnosis of spontaneous abortion and ectopic or normal pregnancy in the first trimester. They concluded that sequential measurements of CA 125 appear to be a good sensitive prognostic marker in patients with threatened abortion (29).

There are several limitations in our study. First, we did not evaluate the pathologic materials of patients with missed abortion. Therefore, we could not compare the serum and decidual or fetal CA 125 levels. Second, repeated measurements of CA 125 levels in the MA group should be conducted after intervention. This may give an idea about the antigen origin. Further expanded and well-established studies are needed for early diagnosis and prognosis.

In conclusion, the aim of our study was to determine if missed abortion can be determined or recognized at the first admission using routine hematologic tests in asymptomatic pregnant women. Second, we investigated the diagnostic value of CA 125 in predicting missed abortion. We found low sensitivity of CA 125 and hematologic inflammatory markers, such as MPV and NLR, in patients with MA. Of all hematologic inflammatory markers, higher RDW was the only marker associated with MA. RDW is a low-cost, widely available marker and may be a promising prediction factor of MA.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - G.U., G.A.; Design - G.U., F.Ç.; Supervision - H.Aksoy, H.Akkaya; Resource - G.A., E.K.; Materials - E.K.; Data Collection and/or Processing - G.U., F.Ç., E.K., H.Akkaya; Analysis and/or Interpretation - G.U., H.Akkaya; Literature Search - G.U., H.Aksoy; Writing - G.U.; Critical Reviews - H.Aksoy, G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Erciyes Üniversitesi Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - G.U., G.A.; Tasarım - G.U., F.Ç.; Denetleme - H.Aksoy, H.Akkaya; Kaynaklar - G.A., E.K.; Malzemeler - E.K.; Veri Toplanması ve/veya İşlemesi - G.U., F.Ç., E.K., H.Akkaya; Analiz ve/veya Yorum - G.U., H.Akkaya; Literatür Taraması - G.U., H.Aksoy; Yazıyı Yazan - G.U.; Eleştirel İnceleme - H.Aksoy, G.A.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Uysal G, Çağlı F, Karakılıç EÜ, Akkaya H, Aksoy H, Açmaz G. The efficacy of haematologic parameters in the diagnosis of missed abortus. Eur J Ther 2018; 24: 17–21