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Mean Platelet Volume increase in Endometriomas and Benign Ovarian Cysts: A prospective case-controlled study

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ABSTRACT

Objective: The aim of this research is to compare mean platelet volumes (MPV) among women with ovarian endometriomas, women with benign ovarian cysts and infertile women who were otherwise healthy.

Material and Methods: Women were selected for the ovarian endometrioma and benign ovarian cyst group after laparoscopic ovarian cyst excision and confirmed histopathologic evaluation. The control group was assigned from women with male partner infertility or unexplained infertility but who were otherwise healthy. Mean platelet volume calculated as a part of complete blood count, which collected in potassium ethylenediaminetetraacetic acid tubes

Results: There were 98 women in the endometrioma group, 94 in the benign cyst group and 99 in the control group. Mean platelet volume was different among the groups ($p<0.01$). The mean platelet volume in the infertile group was statistically different than in the endometrioma and benign cyst groups and was similar between the endometrioma and benign cyst groups. When compared with the infertile group, the area under the curve and predictive value of the mean platelet volume for the endometrioma and the benign cyst group were 0.73 ±0.03 fl ($p<0.01$, CI 0.65-0.80) and 0.72±0.06 fl ($p<0.01$; CI 0.64-0.79), respectively. Mean platelet volume had a sensitivity of 74% and specificity of 63% for endometrioma and sensitivity of 72%, and specificity of 63% for benign cysts at a cut-off point of 9.05 fl.

Conclusion: The present study demonstrated that mean platelet volume was increased in women with ovarian endometriomas and benign cysts and showed predictive values for endometriomas and benign ovarian cysts.

Keywords: Mean platelet volume, endometrioma, ovarian benign cyst, sensitivity, specificity

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INTRODUCTION

Platelets are blood products without a nucleus that are produced by megakaryocytes in the bone marrow and then released into the bloodstream. It has long been known that the main function of platelets is to stop bleeding from injured vessels. Recent studies have reported that platelets are multifunctional and are the first blood products to accumulate at the site of an injury (**1**). Platelets participate in a variety of tasks to maintain an individual's health, including hemostasis, inflammation, immune response, complement system activation, microbial host defense, angiogenesis, the metastatic process, wound healing and remodeling (**1, 2, 3**). Since the discovery that platelets are multifunctional, many studies have been performed to evaluate whether platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW) have value in disease diagnosis and progression and whether they could be used as prognostic factors (**3,4,5,6**).

In inflammatory conditions, interleukins, including interleukine-1 (IL-1), interleukin-3 (IL-3), interleukin-6 (IL-6), and engrossing tumor factor -α (TNF-α), are released into the bloodstream. Interleukins activate platelets, and activated platelets became larger, which leads to increased MPV. Interleukin-6 has a dual action: first, it may stimulate the liver to produce thrombopoietin, which in turn stimulates megakaryocytes to produce to young platelets; second, IL-6 directly stimulate the megakaryocytes, leading to the production and release of young platelets, which have a high cytoplasmic volume and more granular particles. Both of these action results in an increase of MPV (**7, 8**). When platelets are activated as part of the immune response, they release inflammatory mediators, which leads to the aggregation of immune cells in the inflamed area (**7**). Immune cells in the inflamed area also release inflammatory mediators, leading to enhanced platelet production and activation and an increase of MPV. Based on the knowledge that MPV is affected during inflammatory conditions, MPV has been studied and evaluated as a marker for inflammatory diseases such as ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, and acute pancreatitis **(9, 10**). The results of these studies suggest that MPV could be used as an inflammatory marker in various diseases (**7,11,12,13**). In light of this knowledge, we conducted a prospective study to compare MPV in patients with endometriomas, patients with Benign ovarian cysts (BOC) other than endometriomas, and patients without ovarian tumour.

MATERIAL and METHODS

This prospective study was conducted between February 2012 and December 2015 at Zekai Tahir Burak Women's Health Education and Research Hospital's Department of Gynecology and Infertility in Ankara, Turkey. The study was approved by the hospital's ethics committee (ethical approval no: 22-02-12/20) and conducted in accordance with the Helsinki Declaration. The written informed consent form was obtained from the participants.

The study comprised three groups: an ovarian endometrioma group, a BOC group, and an infertile but otherwise healthy group as a control. The women in the endometrioma group included patients who presented with pelvic-abdominal pain, and in whom physical examination with ultrasound evaluation in infertility and gynaecology outpatient clinic revealed ovarian cysts that indicated endometrioma. The BOC group included women who presented with complaints of pelvic-abdominal pain or who were incidentally diagnosed during physical and ultrasonographic examinations with ovarian cysts larger than 5 cm in size with an initial diagnosis of a BOC. The patients in both groups underwent laparoscopic cyst excision with pathologic evaluation results reporting benign cysts. The control group included infertile women diagnosed in the infertility clinic with male partner infertility (65 women) or unexplained infertility (34 women) and were otherwise healthy. Women with familial Mediterranean fever (FMF), diabetes mellitus, hyperthyroidism, hypothyroidism, thrombocytopenia, cardiovascular disorders, malignancies, hypertension, peripheral vascular diseases, metabolic diseases, or kidney or liver disease were excluded from the study.

Routine antecubital venous blood samples were obtained from all patients by venipuncture for the laboratory analysis and a complete blood count. The samples were obtained preoperatively in the endometrioma and ovarian cyst group and at the initial evaluation in the infertile control group. Blood samples for the complete blood count (CBC) were placed in potassium ethylenediaminetetraacetic acid (EDTA)–based anticoagulated tubes and were measured by a Beckman Coulter LH 780 Analyzer (Beckman Coulter Inc., USA) within 120 minutes. The platelet count and mean MPV were calculated as part of the routine CBC analysis. The reference range values for the CBC data according to local calibration from our hospital's laboratory were as follows: the MPV was 7.4–10.9 femtoliters (fl), the platelet count was 150–450 $\times 10^3/\mu L$, and the leukocyte count was 4–10.3x$10^3\mu L$.

The SPSS statistical software package (SPSS, version 20 for Windows IBM; SPSS Inc., Chicago, Illinois, USA) was used to perform all statistical calculations. All of the data are expressed as the mean ± SD. A two-tailed p-value < 0.05 was considered significant in all statistical analyses. The comparison of groups were carried out with the one-way analysis of variance (ANOVA) test if the group data was compatible with the parametric test assumptions. If the group data was not compatible with the parametric test assumptions, the comparison of groups were carried out with the Kruskal–Wallis H test. Subgroup analysis was performed with post-hoc tests (Tukey's test for ANOVA, the Games–Howell test for Kruskal–Wallis) in the presence of differences among groups. Comparison of MPV among groups was carried out with the Kruskal–Wallis H test because the distribution of variances is not homogeneous among groups. Receiver operating characteristic (ROC) curves were constructed by plotting the values for MPV. The inflection points for the ROC curves used as cut-off values for the identification of endometrioma and BOC; sensitivity and specificity for cut-off values calculated, and $p < 0.05$ with 95% confidential intervals (CIs) not crossing 1 were considered statistically significant.

RESULTS

The study comprised 291 women, with 98 women in the ovarian endometrioma group, 94 women in the BOC group, and 99 women in the infertile group. The patients' ages, body mass indexes (BMIs), and leukocyte and platelet counts were similar among the groups ($p = 0.45$, $p = 0.33$, $p = 0.18$, and $p = 0.67$, respectively). The MPV was different among the groups ($p<0.01$). Subgroup analyses were performed with the Games–Howell test for MPV. When the endometrioma group was compared with the BOC group, the result was statistically insignificant between the groups ($p = 0.96$). The comparison of the endometrioma group with the infertile group regarding MPV was statistically significant ($p<0.01$). Comparing the infertile group with the BOC group yielded statistically significant results between the groups ($p<0.01$). The characteristics of the groups and the results of the statistical analyses presented in Table 1.

The predictive value of MPV was assessed for both the ovarian endometrioma and BOC groups with ROC curves (Figures 1 and 2, respectively).

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When ROC curves were compared between the endometrioma and infertile groups, the area under the curve was 0.63 ± 0.03, which was statistically significant (p<0.01; 95% CI: 0.54–0.68). The cut-off point for endometrioma in the ROC curve was 9.55 with a sensitivity of 59% and a specificity of 60%.

When the ROC curves were compared between the BOC group and infertile groups, the area under the curve was 0.61 ± 0.03, which was statistically significant (p<0.01; 95% CI: 0.54–0.68). The cut-off point for BOC in the ROC curve was 9.55 with a sensitivity of 57% and a specificity of 59%.

Table 1. The feature of the groups and results of statistical analyses

Features	Endometrioma (n= 98)	BOC (n=94)	Infertility (n=99)	p
Age (year)	29.7±6.7	30.5± 8.1	28.2± 4.7	0.45
BMI kg/m^2	25.8±3.8	26.6±3.7	26.2±4.3	0.33
Leucocytes (x10^3 mm^3)	6.9±1.5	7.1±1.5	7.3±1.5	0.18
Platelets (x10^3 mm^3)	262±57	269±68	269±61	0.67
MPV (fL)	9.9±1.2	9.7±1.3	8.9±0.8	0.00

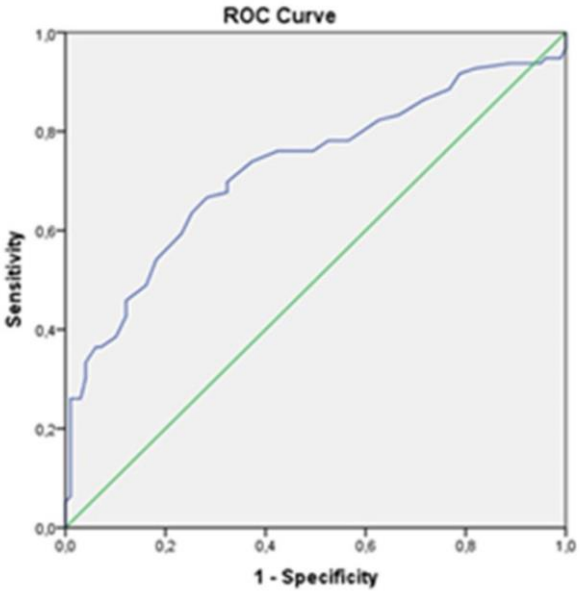

Figure 1. The receiver operator curve of the ovarian endometriomas group.

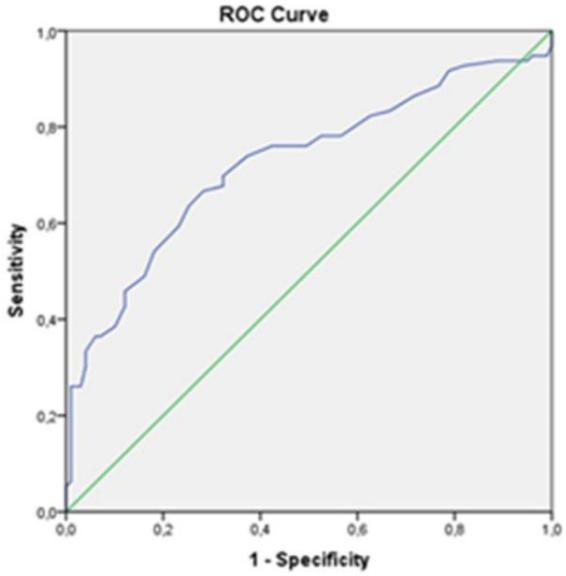

Figure 2. The receiver operator curve of the benign ovarian cyst group.

DISCUSSION

The present study showed that MPV was higher in the patients with endometriomas and patients with Benign ovarian cysts (BOC) than in infertile but otherwise healthy women, and MPV had predictive value for endometriomas and BOC. The increased MPV in patients with endometriomas and BOC can be explained in two ways. First, ovarian cysts apply constant pressure to the ovarian tissue, which causes cells to stretch and atrophy; this leads to the release of inflammatory cytokines and initiates the release of inflammatory mediators, which creates inflammatory conditions in the ovary (**14, 15**). Second, ovarian cysts distort the shape and course of the ovarian arteries, resulting in pressure on the vessels (**16**). Both of these pathways lead to the development of hypoxia in the ovarian tissues. In hypoxic conditions, the ovarian cells release proinflammatory cytokines and chemokines (**17,18**). Inflammation mediators lead to platelet release by megakaryocytes as well as the initiation of platelet activation and the aggregation of platelets in the inflamed tissue. The production of platelets by megakaryocytes and their activation by inflammatory mediators increases platelet volume, which results in an increase of MPV (**2,3,7**).

High-grade inflammatory conditions, such as active rheumatoid arthritis and attacks of FMF, are associated with the circulation of predominantly small platelets due to the rapid consumption of large-size platelets at the inflammatory site (**19**). In contrast, chronic inflammatory diseases are characterized by large-size platelets (and increased MPV) in the circulation (**19**). During a chronic inflammation process, platelet consumption is slow, and inflammatory mediators constantly stimulate platelet release and the activation of platelets, resulting in an increase of MPV. Our study results are in accordance with previous studies and showed that MPV was higher in patients with endometrioma and patients with BOC than in infertile but otherwise healthy women. Endometrioma and other types of BOC are chronic, progressive inflammatory conditions that lead to the constant production of inflammatory cytokines, resulting in the release of a high volume of platelets and the activation of platelets.

Yavuzcan et al. compared MPV among patients with advanced-stage (stage 3/4) endometriosis with endometrioma (OMA), patients with a non-neoplastic adnexal mass other than endometrioma (non-OMA), and control patients. They found that MPV was similar among the groups, and the differences among the groups were statistically insignificant (**20**). On the other hand, in their retrospective study, Turgut et al. compared the level of MPV in patients with endometriosis with the level of MPV in healthy women. They found that MPV was higher in the endometriosis group, and the difference was statistically significant (**21**). Yildirim et al. reported in their clinical research that MPV was not statistically different between patients with ovarian cancer and patients with benign ovarian tumours (**22**). Qin et al. reported that MPV was not statistically different between benign ovarian tumours and the control group, but MPV was lower in patients with ovarian cancer compared with patients with benign ovarian tumours and the control group (**23**). Our study showed that MPV was higher in patients with endometriomas and patients with BOC. In light of the explanation provided above, the differences in the results of these studies have a plausible explanation. Endometriomas and BOC cause chronic hypoxic conditions in the ovary by exerting constant pressure on the ovarian tissue as well as pressure and distortion of the ovarian vessels. In hypoxic conditions, ovarian cells such as endothelial cells and fibroblasts could release hypoxic-ischemic factor (HIF) (**18**). HIF initiates inflammatory cytokine synthesis and releases cytokines into the blood circulation. Inflammatory cytokines stimulate the production of young, high-volume platelets by megakaryocytes and activated platelets in the bloodstream. Together, these processes result in an increase of MPV in the bloodstream.

CONCLUSIONS

In conclusion, the present study demonstrated that MPV was higher in both endometriomas and BOC and had predictive value. MPV calculated as part of a CBC, which is simple and inexpensive. When the cut off value is determined as 9.55 fl, MPV can be used as a marker in patients with endometriomas and patients with BOC. Although our study shows that MPV is an important biomarker in the diagnosis of endometriomas and BOC. Our findings should be supported by further studies.

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