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Original Article

The clinical significance of classical and new emerging determinants of adenomyosis

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Abstract: Objective: The present study aims to analyze the diagnostic accuracy of clinical characteristics together with new emerging laboratory markers of adenomyosis. Methods: This study was a retrospective analysis of clinical and laboratory characteristics of 99 women who underwent hysterectomies with (study group) or without (control group) a diagnosis of adenomyosis, 56 and 43 patients in each group, respectively. Results: The women with adenomyosis were more likely to have younger age (OR = 1.14, 0.789-0.971 95% CI, P = 0.010), higher parity (OR = 1.81, 0.308-0.988 95% CI, P = 0.046), higher number of curettage (OR = 1.90, 1.189-3.041 95% CI, P = 0.007), dysmenorrhea (OR = 117.49, 2.715-5084.883 95% CI, P = 0.013) and elevated mean platelet volume (OR = 5.17, 2.054-13.028 95% CI, P = 0.000). After receiver-operating-characteristics curve analysis, using a cut-point of 8.5 fL, the preoperative mean platelet volume predicted adenomyosis with a sensitivity of 56.6% and specificity of 82.6%. Conclusions: Those findings suggest gynecologists to give priority on adenomyosis when premenopausal paraous patient with a history of curettages admitted with a complaint of dysmenorrhea and elevated levels of MPV.

Keywords: Adenomyosis, dysmenorrhea, mean platelet volume

Introduction

Adenomyosis is classically described as "the benign invasion of endometrium into the myometrium, resulting in a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium" [1]. It is yet unclear why adenomyosis arises in some women and not in others. There are questions concerning factors that control the development and alignment at the endometrial-myometrial interface (basal membrane). This is particularly relevant because the endometrium lacks submucosa and basal membrane [1] and also a local microtraumatization takes place at the endometrial-myometrial interface, caused by a direct trauma (birth, cesarean section, curettage), chronic uterine peristaltic activity or phases of hyper peristalsis. Those local traumas lead activation of the mechanism of 'tissue injury and repair' (TIAR) [2]. The infiltrative growth of endometrium and chronic inflammation precedes this activated mechanism. It was shown that the interaction of macrophages with activated platelets at sites of inflammation during the injury and repair process results in induced cytokine secretion from these macrophages and platelets [3]. Macrophages, platelets and some cytokines derived from macrophages and platelets are suggested to be in contribution with the development of endometriosis and adenomyosis by promoting neovascularization, inflammation and attachment of endometrial cells [4, 5].

Mean platelet volume is a platelet feature that indicates the size and activity of platelets. It is a newly emerging marker of diseases in which chronic and low-grade inflammations have a role in their pathophysiological mechanisms [6,

7]. Large platelets contain more dense granules and produce large amounts of inflammatory cytokines and chemokine as a result of activation and stimulation [8].

Histopathological examination of surgical specimens has been accepted as the gold standard for identifying adenomyosis [9]. A useful and cost effective peripheral, preoperative marker for evaluation of patients with adenomyosis is needed. In the present study we try to identify the diagnostic efficacy of known clinical characteristics together with new emerging biomarkers of chronic inflammation displayed in CBC hand-outs on preoperative diagnosis or clinical suspicion of adenomyosis. Displaying the significance of those characteristics may facilitate the diagnostic process of this unique disease.

Materials and methods

The present study was approved by and conducted at the Institutional Review Board and Ethical Committee of Haydarpasa Research and Education Hospital of Gulhane Military Medicine Academy.

This was a retrospective analysis of 99 hysterectomies, which were consecutively performed at the study center. This was a retrospective analysis of 99 hysterectomies which were consecutively performed at the study center between the calendar years 2005 and 2008. Study group was consist of 56 patients diagnosed as having adenomyosis alone or concomitant with other uterine pathologies according to the histopathological evaluation of the surgical specimens. The remaining 43 women who were free from a diagnosis of adenomyosis served as the control group.

Data were acquired from medical records that related to the following: age gravidity, parity, curettage, menstrual duration, delivery route, smoking habit, family history, menopausal status, exogenous hormone use (estrogen, progesterone or postmenopausal hormone replacement therapy), clinical signs (menorrhagia, dysmenorrhea, chronic pelvic pain, infertility, adnexial mass and pelvic prolapse), complete blood count parameters and histopathological findings (uterine fibroids, endometriosis, endometrial polyp, endometrial hyperplasia, endometrial cancer or ovarian tumor).

Complete blood count

The CBC results obtained in the first month of preoperative period were used in the study. All blood samples were obtained by standard phlebotomy method and collected in the EDTA containing CBC tubes. All CBC analysis was performed by monthly calibrated automated commercial counter (Coulter counter®, Max Instruments Laboratory, Milan, Italy).

Histopathological evaluation

All included 99 hysterectomy specimens were re-evaluated by a pathologist. During this evaluation a uniform diagnostic standard was used to define adenomyosis in specimens. The presence of endometrial glands and stroma within the myometrium in more than one low power field away from the endomyometrial junction was adopted for diagnosis of adenomyosis during this evaluation.

Exclusion criteria

The patients with factors that could interfere with the CBC/Platelet counts were excluded.

A. The factors related with sample collection: The patients with a time interval more than two hours between the time of sample acceptance and the time of sample report were excluded from the study.

B. The patient-related factors: The patients considered as high risk patient according to anesthesia reports after appropriate systemic evaluation were excluded from the study.

Statistical analysis

Collected data were analysed by a Statistical Package for Social Sciences version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were denoted as numbers or percentages where appropriate. The Smirnov-Kolmogorov test was used to test the distribution of data. Student t-test and Mann-Whitney U test were used to compare the continuous variables, while chi-square test was used to compare the categorical variables of the adenomyosis and control groups. Logistic regression analysis was carried out to determine the variables that were

Table 1. Demographic and Clinical Characteristics of Adenomyosis and Control Groups

	Adenomyosis (n = 56)	Control Group (n = 43)	P
Age (years)	51.48 ± 7.76	57.86 ± 11.06	0.005*
Gravidity	4.68 ± 2.30	3.91 ± 3.61	0.019*
Parity	2.55 ± 1.02	2.42 ± 1.91	0.240
Curettage	2.05 ± 1.89	1.28 ± 2.18	0.003*
Smoking	12/44 (21.4.0%)	12/31 (27.9%)	0.456
Exogenous estrogen use	3 (5.4%)	0 (0.0%)	0.255
Exogenous progesteron use	12 (21.4%)	11 (25.60%)	0.628
Menopause	15 (26.8%)	24 (55.8%)	0.003*
Menorrhagia	41 (73.1%)	25 (58.1%)	0.115
Dysmenorrhea	54 (96.4%)	39 (90.7%)	0.236
Chronic pelvic pain	23 (41.1%)	19 (44.2%)	0.756
Infertility	0 (0.0%)	2 (4.7%)	0.103

*P < 0.05 was accepted to be statistically significant.

Table 2. Indications of hysterectomies

	Adenomyosis (n = 56)	Control Group (n = 43)	P
Uterine fibroids	38 (67.9%)	22 (51.2%)	0.090
Endometriosis	2 (3.6%)	1 (2.3%)	1.000
Endometrial polyp	18 (32.1%)	4 (9.3%)	0.007*
Endometrial hyperplasia	9 (16.1%)	1 (2.3%)	0.004*
Adnexial mass	18 (32.1%)	9 (20.9%)	0.214
Ovarian carcinoma	1 (1.8%)	2 (4.7%)	0.578
Pelvic prolapse	2 (3.6%)	8 (18.6%)	0.010*
Cervical cancer	1 (1.8%)	0 (0.0%)	1.000

*P < 0.05 was accepted to be statistically significant.

independently associated with adenomyosis within 95% confidence interval (CI). A two-tailed *p* value less than 0.05 was accepted as statistically significant.

The capacity of serum MPV value in predicting presence of adenomyosis was analyzed using Receiver Operating Characteristics (ROC) Curve analysis. When a significant cut-off value was observed, the sensitivity, specifity, positive and negative predictive values were presented. While evaluating the area under the curve, a 5% type-1 error level was used to accept a statistically significant predictive value of the test variables.

Results

Table 1 demonstrates the demographic and clinical characteristics of the adenomyosis group (n = 56) and control group (n = 43). The women with adenomyosis were of a significantly younger age (P = 0.005), higher gravidity (P = 0.019) and higher number of curettage (P = 0.003). When compared with the control group, menopausal status and pelvic prolapse were significantly less frequent in the adenomyosis group (P = 0.003 and P = 0.01, respectively). While, endometrial polyps and endometrial hyperplasia were significantly more frequent in the adenomyosis group (P = 0.007 and P = 0.04 respectively), menorrhagia and uterine fibroid frequency were similar within the two groups (P = 0.115 and P = 0.09 respectively) (Table 2).

Table 3 shows complete blood counts of the adenomyosis and control groups. Leukocyte count, neutrophil count, lymphocyte count, mean platelet volume (MPV) and platelet distribution width (PDW) were significantly higher in the adenomyosis group (P = 0.028, P = 0.09, P = 0.012, P = 0.007 and P = 0.000 respectively).

A logistic regression model was built with 16 variables: age, gravidity, parity, curettage number, menstrual duration, menopausal state, dysmenorrhea, menorrhagia, chronic pelvic pain, pelvic prolapse, fibroids, endometrial polyps, endometrial hyperplasia, adnexal mass, MPV and PDW). The best backward binary logistic regression model was established with six significant variables at the sixth step of the model. The women with adenomyosis were more likely to be of younger age (OR = 1.14, 0.789-0.971 95% CI, P = 0.010), higher parity (OR = 1.81, 0.308-0.988 95% CI, P = 0.046), higher number of curettage (OR = 1.90, 1.189-3.041 95% CI, P = 0.007), dysmenorrhea (OR = 117.49, 2.715-5084.883 95% CI, P = 0.013) and elevated MPV (OR = 5.17, 2.054-13.028 95% CI, P = 0.000). The women with adenomyosis were less likely to suffer from uterine pro-

Table 3. Complete blood counts of adenomyosis and control groups

	Adenomyosis (n = 56)	Control Group (n = 43)	P
White blood cells (/μL)	7.77 ± 2.86	7.12 ± 1.88	0.028*
Neutrophils (/μL)	60.94 ± 14.91	61.31 ± 7.50	0.009*
Lymphocytes (/μL)	28.82 ± 11.65	29.85 ± 6.55	0.012*
Monocytes (/μL)	7.64 ± 4.23	6.49 ± 1.80	0.231
Eosinophils (/μL)	2.03 ± 1.72	1.74 ± 1.36	0.751
Basophils (/μL)	0.54 ± 0.69	0.58 ± 0.31	0.012*
Red blood cells (K/μL)	4.39 ± 0.50	4.41 ± 0.42	0.205
Hemoglobin (g/dl)	12.33 ± 1.50	12.68 ± 1.58	0.674
Hematocrit (%)	36.90 ± 4.14	38.15 ± 4.39	0.559
Mean corpuscular volume (fl)	84.25 ± 7.48	86.39 ± 6.32	0.235
Mean corpuscular hemoglobin (pg)	28.27 ± 3.02	28.75 ± 2.44	0.191
Mean corpuscular hemoglobin concentration (g/dl)	33.39 ± 1.24	40.42 ± 4.72	0.482
Red cell distribution width (%)	14.77 ± 2.55	14.60 ± 2.06	0.824
Platelets (K/μL)	261.66 ± 60.00	285.88 ± 80.36	0.181
Plateletcrit (%)	0.22 ± 0.04	0.22 ± 0.07	0.161
Mean platelet volume (fl)	8.75 ± 1.14	7.82 ± 0.82	0.007*
Platelet distribution width (%)	16.43 ± 0.78	15.86 ± 0.52	0.001*

*P < 0.05 was accepted to be statistically significant.

Table 4. Multivariate logistic regression model for adenomyosis and related factors

	OR	P	95.0% C.I. for EXP (B)	
Age	1.14	0.012	0.789	0.971
Parity	1.81	0.046	0.308	0.988
Dilatation and curettage	1.90	0.007	1.189	3.041
Dysmenorhea	117.49	0.013	2.715	5084.883
MPV	5.17	0.000	2.054	13.028
Uterine prolapse	13.3	0.010	0.011	0.532

The sensitivity and specificity of this model were 85.7% and 79.1% respectively.

lapse (OR = 13.3, 0.011-0.532 95% CI, P = 0.010). The sensitivity and specificity of this model were 85.7% and 79.1%, respectively (**Table 4**).

For observed significant cut-off values of MPV, the sensitivity, specificity, positive and negative predictive values as presented in **Table 5** and **Figure 1**.

Discussion

Until recently, adenomyosis has been diagnosed only through histological examination of the surgical specimens. In other words, hysterectomy is required for the diagnosis of adenomyosis and many asymptomatic cases are missed. Some recent studies have begun to show importance of chronic inflammatory processes and its biomarkers on the pathogenesis and development of adenomyosis [10, 11]. Among those many biomarkers, components of complete blood count (CBC) seem to be very important, as they are quite easily accessible and cost effective parameters. According to those reports that were giving a crucial role to immune system and chronic inflammation in disease process the key point is the activation of TIAR mechanism by local micro-traumatization effect of chronic uterine peristaltic activity at the endometrial-myometrial interface [2]. The activation of TIAR mechanism is followed by initiative growth together with chronic inflammation and the platelets are activated as a part of this systemic immune response and exert their pro-inflammatory effects [12]. The activated platelets tend to be larger and contain more dense granules to produce large amounts of inflammatory cytokines and chemokine [8]. While MPV is a parameter showing the mean volume of platelets in the circulation, PDW is a parameter showing distribution wideness of the volumes of those platelets in the CBC hand-outs. MPV

Table 5. The sensitivity, specifity, positive and negative predictive values for observed significant cut-off values of MPV

	Thres hold value	Sensitivity	Specifity	PPV	NPV	Area	SE	P	95% CI
MPV	8.07	0.716	0.695	0.80	0.615	0,751	0,049	< 0,001	0,66-0,84
	8.59	0.566	0.826	0.789	0.622				

*ROC Curve analysis.

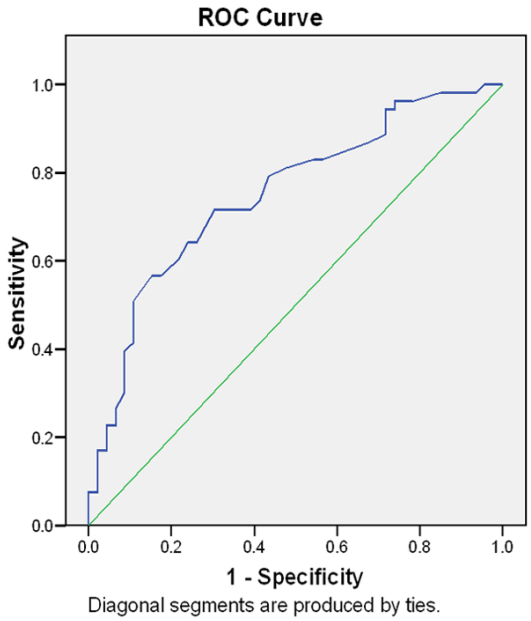

Figure 1. Area under the curve of significant cutt-off value for MPV.

and PDW were also found to be the clinical marker of disease activation, progression and responses to various treatment options in many other chronic inflammatory diseases like DM, rheumatoid arthritis, ischemic stroke and myocardial infarction. Complying with literature, this study shows that leukocyte count, PDW and MPV were significantly higher in the adenomyosis group and women with adenomyosis were five times more likely to have elevated MPV values. According to us, this elevation can be considered to reflect the underlying inflammatory response. To the best of our knowledge, this is one of the pioneer studies to report a probable link between an elevated MPV/PDW and adenomyosis.

At the second part of the study, a logistic regression model was built to assess the clinical significance of clinical characteristics and basic laboratory findings on preoperative diagnosis of adenomyosis. For this purpose statistically significant study parameters and the parameters assumed to be effective on diagnosis were assessed in the regression model. We found it not right to assess two similar parameters like MPV and PDW on the same regression model. Due to the higher number of previous reports, we chose to assess the significance of MPV in this model. The sensitivity and specificity of this model were 85.7% and 79.1% respectively.

A ROC curve analysis was built to define a reliable the cut-off value for MPV values. This ROC curve showed us, the MPV values higher than 8 fl. and/or 8.5 fl could be accepted as a sign of this elevation in volume of platelets.

According to this model, younger age, higher parity, higher number of curettage, dysmenorrhea, together with elevated MPV values were found to be significant indicators for preoperative diagnosis of adenomyosis. Especially, dysmenorrhea was found to be 56 times more frequent with adenomyosis. However, menorrhagia was observed as a common complaint of cases requiring hysterectomy, rather than a specific complaint of adenomyosis. A retrospective study analysing 710 premenopausal patients undergoing hysterectomy reported that dysmenorrhea was the most common complaint, occurring in 81.7% of the patients. And also, it was reported that dysmenorrhea co-occurred most frequently with menorrhagia [13-16]. While increased prostaglandin production was blamed for dysmenorrhea, increased peripheral vascularity of endometrium was thought to be responsible from menorrhagia commonly seen in adenomyosis [17]. Increased MPV could have played a crucial role in the pathophysiological mechanisms beneath the symptom of dysmenorrhea and menorrhagia. Higher MPV value refers to larger platelets which have a greater content of granules. These granules usually consist of vasoactive substances which include thromboxane synthesis, beta-thromboglobulin secretion, sero-

tonin release, expression of P-selectin, glycoprotein IIb/IIIa and fibrinogen receptors. As the secretions of these cellular mediators (especially thromboxane) are enhanced, vasoconstriction may occur and this may eventually lead to uterine cramps [18, 19]. And also, larger platelets are more likely to make up thrombi that are resistant to anti-thrombolytic resistant agents. Thus, a higher MPV may correspond to the increased number of both platelet-leukocyte and platelet-platelet aggregates. These microscopic aggregates may cause the interruption of the perfusion provided by uterine vasculature and somehow contribute to the dysmenorrheal symptoms [18, 20].

It is a well-known fact that that adenomyosis was associated with oestrogen dependent pathologies through a pathophysiologic mechanism associated with cytochrome P450 enzyme system. Uterine fibroids, endometriosis, endometrial hyperplasia and endometrium cancer were all known as estrogen dependent diseases and possibly good examples for this assumed association [21]. In this study, while the co-occurrence incidence of adenomyosis with endometriosis, uterine fibroids and endometrium cancer was found to be insignificant, incidence of endometrial hyperplasia was found to be significantly high in specimens with adenomyosis. According to us, those results of this study were under the influence of relatively younger age of the study population. As the endometrial hyperplasia is a well-known precursor lesion of endometrial cancer and estrogen dependent pathology, we are still in line with the hypothesis suggesting estrogen dependent pathophysiological mechanisms had a crucial role on the development of adenomyosis.

Clinicians must bear in mind that MPV is associated with many confounding factors. Thrombocytopenia, different measurement techniques and disease specific or related confounders (gastritis, diabetes mellitus, metabolic syndrome, rheumatoid arthritis etc.) or some other important cardiovascular confounders (smoking, obesity, hypertension, hypercholesterolemia, coronary artery disease, and stroke) can yield MPV results varying up to 40% [18, 22, 23]. It was hard to eliminate or control all those confounders in a retrospective study. As an attempt to control the possible confounders, instead of eliminating patients with some specific diseases, we excluded all the patients with a high anaesthesia risk after systemic evaluation. And also, the samples studied more than two hours after acceptance were excluded as the samples could be affected from EDTA in a time related manner. Therefore, further prospective researches are warranted to clarify the role of MPV in the pathogenesis of adenomyosis by taking consideration all those possible confounders with a larger cohort size.

Although it would be incorrect to make interpretations by the findings of this study to whole adenomyosis patients, we offer gynecologists to give priority to adenomyosis in the diagnostic and treatment process, when premenopausal women applied with a history of multiple births and curettages with concomitant complaint of dysmenorrhea and with elevated MPV values.

Disclosure of conflict of interest

None.

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