

## ORIGINAL RESEARCH

Medicine Science 2017;6(4):717-20

# Considerations on pathophysiology of primary dysmenorrhea under the light of alterations in complete blood count parameters

Serkan Bodur<sup>1</sup>, Mine Kanat Pektaş<sup>2</sup>, Vuslat Lale Bakır<sup>3</sup>, Mehmet Ferdi Kinci<sup>1</sup>, Ibrahim Alanbay<sup>1</sup>,  
Ozgur Dunder<sup>4</sup>

<sup>1</sup>Health Sciences University, Gulhane Training and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

<sup>2</sup>Afyon Kocatepe University Medical Faculty Hospital, Department of Obstetrics and Gynecology, Afyon, Turkey

<sup>3</sup>Haseki Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey

<sup>4</sup>Istanbul Bilim University, Kadikoy Florence Nightingale Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey

Received 30 May 2017; Accepted 05 June 2017

Available online 13.06.2017 with doi: 10.5455/medscience.2017.06.8648

### Abstract

The present study strives to evaluate how the components of complete blood count are altered in women with primary dysmenorrhea. This is a cross-sectional analysis of 155 women with primary dysmenorrhea and 155 women without dysmenorrhea. The primary dysmenorrhea and control groups were matched with respect to age and body mass index. When compared with the controls, the women with primary dysmenorrhea had a significantly younger menarche age, longer menstrual duration, higher leukocyte counts, higher neutrophil counts, and elevated MPV values ( $p=0.010$ ,  $p=0.022$ ,  $p=0.014$ ,  $p=0.011$  and  $p=0.04$  respectively). The logistic regression analysis demonstrated that women with primary dysmenorrhea were more likely to have a younger menarche age (OR=2.14, 95% CI=0.971-3.346,  $p=0.018$ ), longer menstrual duration (OR=1.91, 95% CI=0.988-2.308,  $p=0.044$ ), higher leukocyte counts (OR= 2.90, 95% CI=1.040-3.788,  $p=0.007$ ), and elevated MPV values (OR=3.17, 95% CI=2.056-9.128,  $p=0.001$ ). The sensitivity and specificity of this model were 84.6% and 77.3%, respectively. Leukocytosis and increased MPV are might be associated with the inflammatory and vasoconstrictory pathogenesis of primary dysmenorrhea, but this result should be confirmed in the future researches.

**Keywords:** Dysmenorrhea, mean platelet volume, platelet distribution width

### Introduction

Dysmenorrhea is the most common gynecologic complaint and the leading cause of recurrent short-term school and work absenteeism among adolescent and young adult females [1,2]. Dysmenorrhea in adolescents and young adults is usually primary, and is associated with normal ovulatory cycles and with no pelvic pathology. Thus, it becomes more prevalent during mid and late adolescence as ovulatory menstrual cycles are established. On the other hand, pelvic abnormalities such as endometriosis or uterine anomalies may be found in approximately 10% of females with severe dysmenorrhea symptoms [3,4]. Although lower abdominal cramping is the most common dysmenorrhea symptom, many adolescents and young adults also suffer from other menstruation-associated symptoms, such as headaches, nausea, vomiting and abdominal bloating. Symptoms typically accompany the start of menstrual flow or occur within a few hours before or after onset and last for the first 24 to 48 hours [5,6].

The severity of dysmenorrhea symptoms positively correlates with early menarche, increased duration and amount of menstrual flow, and cigarette smoking, which may presumably increase duration of dysmenorrhea due to nicotine-induced vasoconstriction [7,8]. Premenstrual symptoms, which frequently begin at the third decade of life, are less common in adolescent girls and are often alleviated by adequate treatment of dysmenorrhea [9].

It has been hypothesized that local and systemic symptoms associated with dysmenorrhea occur as a result of the inflammatory response, which is mediated by potent prostaglandins and leukotrienes [10]. Leukocyte count, mean platelet volume (MPV) and platelet distribution width (PDW) are the components of a complete blood count, and they are usually considered as the indicators of inflammation [11,12]. The present study strives to evaluate how the components of complete blood count are altered in women with primary dysmenorrhea.

### Material and Methods

This case-control study was approved by the Institutional Review Board and Ethical Committee and conducted in five different medical centers participated into the study (Afyon Kocatepe University Medical Faculty Hospital, and Haseki Education and Research Hospital).

**\*Corresponding Author:** Serkan Bodur, Health Sciences University, Gulhane Training and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

**E-mail:** [serkan\\_bodur@yahoo.com](mailto:serkan_bodur@yahoo.com)

The comparative analysis of 310 women who were admitted to the study centers between January 2013 and April 2014. This cohort consists of 155 women who were diagnosed with primary dysmenorrhea and 155 women without dysmenorrhea who served as the control group. The diagnosis of primary dysmenorrhea was mainly built on the basis of clinical features like: onset of menstrual pain shortly after menarche, duration of 48-72 hours menstrual pain starting several hours before or just after the menstrual flow, characteristically reporting the pain as cramp or labor like, complaining a concomitant background constant lower abdominal pain radiating to back or the anterior or medial thigh together with unremarkable pelvic examination and pelvic ultrasonography. The women reporting clinical features of menstrual pain sufficient for diagnosis was accepted as primary dysmenorrhea in the absence of specific pelvic pathology that could lead to dysmenorrhea.

Data related to age, gravidity, parity, height, weight, body mass index, smoking habits and complete blood counts were acquired from medical records. Body mass index (BMI) was calculated according to the following formula:

$$\text{Body mass index (kg/m}^2\text{)} = \text{Weight (kg)} / \text{Height}^2 \text{ (m}^2\text{)}$$

The primary dysmenorrhea group and the control group were matched with respect to age and BMI.

### Complete Blood Count

One sample of 20 ml venous blood was drawn by standard phlebotomy from all subjects. This sample was kept for the evaluation of white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin, red cell distribution width, platelet count, mean platelet volume (MPV) and platelet distribution width (PDW) by means of an automated commercial counter (Coulter counter®, Max Instruments Laboratory, Milan, Italy).

After this sample was conveyed into a sodium citrate tube, it was transported in a temperature-controlled container and collected in plastic provettes (Falcon blue cap) containing 3 ml of 3.8% sodium citrate dihydrate and 136 mM glucosium. Time intercourse between sampling and tube reading was never more than two minutes. The samples were read three times, and the final result represents the mean of the three readings.

### Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean  $\pm$  standard deviation, whereas categorical variables were denoted as numbers or percentages as appropriate.

The Kolmogorov-Smirnov test was used to test the distribution of data. The Student's t test and the Mann-Whitney U test were used to compare the continuous variables, while the chi-square test was used to compare the categorical variables of the primary dysmenorrhea group and the control group. Logistic regression analysis was carried out to determine the variables which were independently associated with adenomyosis within a 95% confidence interval (CI). A two-tailed p value of less than 0.05 was accepted to be statistically significant.

### Results

The primary dysmenorrhea group and the control group were matched with respect to age and BMI (p=0.418 and p=0.830, respectively). When compared with the controls, the women with primary dysmenorrhea had a significantly younger menarche age and longer menstrual duration (p=0.010 and p=0.022, respectively) (Table 1). As for the complete blood counts, the women with primary dysmenorrhea had significantly higher leukocyte counts, neutrophil counts and MPV values (p=0.014, p=0.011 and p=0.04, respectively) (Table 2).

A logistic regression model was built with nine variables, including age, gravidity, parity, menarche age, menstrual duration, leukocyte count, neutrophil count, MPV and PDW. The best backward binary logistic regression model was established with significant variables at the fifth step of the model.

Subjects with primary dysmenorrhea were more likely to have a younger menarche age (OR=2.14, 95% CI=0.971-3.346, p=0.018), longer menstrual duration (OR=1.91, 95% CI=0.988-2.308, p=0.044), higher leukocyte counts (OR= 2.90, 95% CI=1.040-3.788, p=0.007), and elevated MPV values (OR=3.17, 95% CI=2.056-9.128, p=0.001). The sensitivity and specificity of this model were 84.6% and 77.3%, respectively.

**Table 1.** Sociodemographic Characteristics of the Study Cohort

	Primary dysmenorrhea group (n=155)	Control group (n=155)	p
Age (years)	32.4 $\pm$ 4.3	32.8 $\pm$ 4.9	0.418
Body mass index (kg/m <sup>2</sup> )	23.9 $\pm$ 3.5	23.8 $\pm$ 3.5	0.830
Gravidity	1.2 $\pm$ 0.8	1.1 $\pm$ 0.6	0.488
Parity	0.9 $\pm$ 0.5	0.8 $\pm$ 0.4	0.566
Menarche age (years)	11.4 $\pm$ 2.9	12.5 $\pm$ 3.8	0.010*
Menstrual duration (days)	7.6 $\pm$ 3.2	6.5 $\pm$ 2.7	0.022*
Smoking	9 (5.8%)	11 (7.1%)	0.077

**Table 2.** Complete Blood Counts of the Study Cohort

	Primary dysmenorrhea group (n=155)	Control group (n=155)	p
White blood cells (/μL)	8255.1±2568.2	7611.0±1889.0	0.014*
Neutrophils (/μL)	7504.6±6131.1	6094.8±1491.5	0.011*
Lymphocytes (/μL)	785.8±655.1	882.9±1165.1	0.042
Monocytes (/μL)	564.5±424.0	650.0±180.4	0.231
Eosinophils (/μL)	103.1±172.8	174.4±136.6	0.751
Basophils (/μL)	58.7±31.9	69.6±54.0	0.033
Red blood cells (K/μL)	4392.0±505.4	4298.4±347.2	0.936
Hemoglobin (g/dl)	12.3±1.4	12.2±1.4	0.499
Hematocrit (%)	36.6±3.8	36.5±.5	0.763
Mean corpuscular volume (fl)	85.0±7.1	85.2±7.0	0.766
Mean corpuscular hemoglobin (pg)	28.3±3.2	28.8±2.7	0.266
Mean corpuscular hemoglobin concentration (g/dl)	33.2±1.4	33.5±1.3	0.154
Red cell distribution width (%)	14.9±10.2	14.4±2.2	0.518
Platelets (K/μL)	265.3±75.7	278.1±60.2	0.106
Plateletcrit (%)	0.23±0.04	0.23±0.07	0.266
Mean platelet volume (fl)	9.0±1.1	8.6±1.1	0.004*
Platelet distribution width (%)	16.4±8.8	16.1±1.7	0.659

\*p<0.05 was accepted to be statistically significant

## Discussion

Dysmenorrhea in adolescents and young adults is mainly functional and is attributable to physiological reasons. That is, primary dysmenorrhea is associated with a normal ovulatory cycle and the absence of pelvic pathology. Instead, primary dysmenorrhea is attributed to the predominance of omega-6 fatty acids in the cell wall phospholipids. This predominance is caused by high lipid intake in the diet and the reorganization of fatty acids following ovulation. After the onset of progesterone withdrawal before menstruation, these omega-6 fatty acids, particularly arachidonic acid, are released, and a cascade of prostaglandins and leukotrienes is initiated in the uterus. The response, which is evoked by these potent vasoconstrictors and inflammatory mediators, produces both cramps and systemic symptoms such as nausea, vomiting, bloating, and headaches. In particular, the prostaglandin F2a, a cyclooxygenase metabolite of arachidonic acid, causes potent vasoconstriction and myometrial contractions, leading to ischemia and pain [2-5].

Prostaglandin F2a activity in menstrual fluid was found to be twice as high in the dysmenorrheic women when compared to the women without dysmenorrhea. Moreover, the women with dysmenorrhea receiving no medication had endometrial PGF2a levels four times higher than those of the women without dysmenorrhea on the first day of their menstrual period [12,13]. The uterus is able to synthesize and metabolize leukotrienes and leukotriene receptors that have been detected in uterine tissue. The highest leukotriene concentrations were specified in hysterectomy specimens of adult women with dysmenorrhea. Menstrual flow leukotriene-C4/D4 levels were also related to the severity of dysmenorrheal symptoms in adult women with primary dysmenorrhea. Additionally, urinary excretion of leukotriene-E4 was elevated in adolescent girls with

dysmenorrhea [14,15]. The findings of these previously published studies indicate the possible involvement of prostaglandins and leukotrienes in the pathogenesis of primary dysmenorrhea.

The mechanisms that are involved in uterine contractility and relaxation may also participate in the pathogenesis of dysmenorrhea. It was reported that circulating vasopressin was increased and uterine contractions were induced during menstruation in women with dysmenorrhea. However, the role of vasopressin in the pathogenesis of primary dysmenorrhea remains controversial [16]. Similarly, it is unknown whether low levels of nitric oxide can induce dysmenorrheal symptoms by triggering the vasoconstriction and myometrial contractions [17].

Recently published studies have focused on the important role of MPV as a marker of inflammation, disease activity and efficacy of anti-inflammatory treatment in several chronic inflammatory disorders. For instance, high-grade inflammatory diseases, such as active rheumatoid arthritis or attacks of familial Mediterranean fever, present with low MPV values, and MPV values increase during the course of anti-inflammatory therapy. It seems that the size of circulating platelets is dependent upon the intensity of systemic inflammation [18].

A higher MPV value refers to larger platelets, which have a greater content of granules. These granules usually consist of vasoactive substances that include thromboxane synthesis, beta-thromboglobulin secretion, serotonin release, expression of P-selectin, glycoprotein IIb/IIIa and fibrinogen receptors. As the secretions of these cellular mediators (especially thromboxanes) are enhanced, vasoconstriction may occur, and this may eventually lead to uterine cramps [18,19].

When compared to smaller platelets, larger platelets are more active and more prone to aggregate. This finding may suggest that larger platelets are more likely to make up thrombi that are resistant to anti-thrombolytic agents. Thus, a higher MPV may correspond to an 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 dysmenorrheal symptoms [18,20].

Soydinc et al. were the first to evaluate the hematological parameters of women with primary dysmenorrhea during their menstrual cycle. Both the women with primary dysmenorrhea (n=41) and the women without dysmenorrhea (n=40) were found to be statistically similar with respect to hematological parameters with regard to menstrual phase, follicular phase (days 1-4), follicular phase (days 9-12) and luteal phase (days 21-23). The only exception was the MPV value, which was significantly higher in each phase of the menstrual cycle. Therefore, it has been concluded that primary dysmenorrhea is associated with decreased MPV value, and platelets may participate in the inflammatory pathogenesis of primary dysmenorrhea [21].

In contrast, the findings of the present study demonstrate a significant rise in both the leukocyte count and MPV value. Such a discrepancy may be attributable to the differences in cohort size and the variations in the demographic characteristics of the recruited subjects. Another reason for this contradiction may be the disparity in the methods of MPV measurement. That is, different techniques adopted for the measurement of MPV can yield varying results of up to 40%. Another issue related to the measurement of MPV is the utilization of anticoagulants. Although MPV should be measured by clinical hematology analysts using sodium citrate, MPV is usually measured as a component of a complete blood count within ethylenediaminetetraacetic acid (EDTA) tubes in routine clinical practice. Since the anticoagulant EDTA induces the platelet shape to change, MPV increases in a time-dependent manner, and the measurements become relatively unreliable [22]. Additionally, one of the other major most important limitations of the study is the difficulty to rule out endometriosis which was the leading cause of secondary dysmenorrhea. As the diagnostic golden standard of endometriosis is to confirm diagnosis by laparoscopy, it was almost impossible for us to apply laparoscopy to all participants and to it was also almost impossible to have necessary approvals from the ethical committee.

The findings of the present study imply that leukocytosis and increased MPV are associated with the pathogenesis of primary dysmenorrhea. However, the significance of this study is limited by the relatively small cohort size and the lack of longitudinal data about MPV values throughout the menstrual cycle. However, its case-control design and the utilization of sodium citrate tubes may provide an advantage. Large-scale, prospective, case-control studies are required to clarify the role of MPV in the etiopathogenesis of primary dysmenorrhea.

## References

1. Harada T. Dysmenorrhea and endometriosis in young women. *Yonago Acta Med.* 2013;56(4):81-4.

2. Allen LM, Lam AC. Premenstrual syndrome and dysmenorrhea in adolescents. *Adolesc Med State Art Rev* 2012;23(1):139-63.
3. Harel Z. Dysmenorrhea in adolescents. *Ann N Y Acad Sci.* 2008;1135:185-95.
4. Sultan C, Gaspari L, Paris F. Adolescent dysmenorrhea. *Endocr Dev.* 2012;22:171-80.
5. Morrow C, Naumburg EH. Dysmenorrhea. *Prim Care* 2009;36(1):19-32.
6. Harel Z. Dysmenorrhea in adolescents and young adults: from pathophysiology to pharmacological treatments and management strategies. *Expert Opin Pharmacother.* 2008;9(15):2661-72.
7. Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. *Epidemiol Rev.* 2014;36(1):4-13.
8. Ortiz MI, Rangel-Flores E, Carrillo-Alarcón LC, Veras-Godoy HA. Prevalence and impact of primary dysmenorrhea among Mexican high school students. *Int J Gynaecol Obstet.* 2009;107(3):240-3.
9. Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. *Expert Opin Pharmacother.* 2012;13(15):2157-70.
10. Harel Z. Dysmenorrhea in adolescents and young adults: etiology and management. *J Pediatr Adolesc Gynecol.* 2006;19(6):363-71.
11. Sadik CD, Kim ND, Luster AD. Neutrophils cascading their way to inflammation. *Trends Immunol.* 2011;32(10):452-60.
12. Dmitrovic R, Kunselman AR, Legro RS. Sildenafil citrate in the treatment of pain in primary dysmenorrhea: a randomized controlled trial. *Hum Reprod.* 2013;28(11):2958-65.
13. Mrugacz G, Grygoruk C, Siczynski P, Grusza M, Bolkun I, Pietrewicz P. Etiopathogenesis of dysmenorrhea. *Med Wieku Rozwoj.* 2013;17(1):85-9.
14. Harel Z. A contemporary approach to dysmenorrhea in adolescents. *Paediatr Drugs.* 2002;4(12):797-805.
15. Abu JI, Konje JC. Leukotrienes in gynaecology: the hypothetical value of anti-leukotriene therapy in dysmenorrhoea and endometriosis. *Hum Reprod Update.* 2000;6(2):200-5.
16. Valentin L, Sladkevicius P, Kindahl H. Effects of a vasopressin antagonist in women with dysmenorrhea. *Gynecol Obstet Invest.* 2000;50(3):170-7.
17. Ulrich C, Quillici DR, Schegg K, Woolsey R, Nordmeier A, Buxton IL. Uterine smooth muscle S-nitrosylproteome in pregnancy. *Mol Pharmacol.* 2012;81(2):143-53.
18. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: A link between thrombosis and inflammation. *Current Pharmaceutical Design.* 2011;17(1):47-58.
19. Duygu H, Turkoglu C, Kirilmaz B, Turk U. Effect of mean platelet volume on post-intervention coronary blood flow in patients with chronic stable angina pectoris. *J Invasive Cardiol.* 2008;20(3):120-4.
20. Yasar AS, Bilen E, Yuksel IO, Arslantasi U, Karakas F, Kirbas O, Bilge M. Association between admission mean platelet volume and coronary patency after thrombolytic therapy for acute myocardial infarction. *Turk Kardiyol Dern Ars* 2010; 38(2): 85-9.
21. Soydinc HE, Evsen MS, Sak ME, Ozler A, Turgut A, Gul T. Association between mean platelet volume and different phases of menstrual cycle in primary dysmenorrhea. *Clin Exp Obstet Gynecol.* 2013;40(3):429-32.
22. Dunder O, Yoruk P, Tutuncu L, Eriki AA, Muhcu M, Ergur AR, Atay V, Mungen E. Longitudinal study of platelet size changes in gestation and predictive power of elevated MPV in development of pre-eclampsia. *Prenat Diagn.* 2008;28(11):1052-6.