Association between mean platelet volume and different phases of menstrual cycle in primary dysmenorrhea

H.E. Soydinc, M.S. Evsen, M.E. Sak, A. Ozler, A. Turgut, T. Gul

Department of Obstetric and Gynecology, Dicle University School of Medicine, Diyarbakir (Turkey)

Summary

Purpose: Blood cells play a major role in homeostasis and inflammation. Primary dysmenorrhea (PD) involves the production of prostaglandins and leukotrienes, which cause inflammation in uterine tissue. Aim of this study was to investigate whether there is a relation between complete blood count parameters and PD during the menstrual cycle. *Materials and Methods:* The study included 41 cases diagnosed as primary dysmenorrhea (mean age, 23.02 ± 3.43 years) and 40 individuals who control subject (mean age, 23.76 ± 3.13 years). Hematologic parameters were measured on menstrual phase (day 1-4), follicular phase (day 9-12), and luteal phase (day 21-23) during menstrual cycle. *Results:* There were no statistically differences between hematological parameters of two groups except for mean platelet volume (MPV). MPV of PD and control groups at each phase of menstrual cycle were 7.71 vs 8.61 (p = 0.01); 7.66 vs 8.56 (p = 0.005); 7.75 vs 8.53 (p = 0.01), respectively. *Conclusion:* PD is associated with decreased MPV and platelets may be involved in the inflammatory process of PD.

Key words: Primary dysmenorrhea; Complete blood cell count; Mean platelet volume.

Introduction

Primary dysmenorrhea (PD) is defined as a cyclic pain, which begins with menstrual blood flow, or just before, without any evident pathology in pelvic examination. The prevalence of PD is estimated at 25% of women and up to 90% of adolescents [1]. The pathogenesis of PD involves the production of prostaglandins and leukotrienes, both derived from arachidonic acid, which is released as a result of cell destruction in the endometrial tissue due to progesterone withdrawal just prior to menstruation [2]. The inflammation which is caused by the leukotrienes and prostaglandins, creates both uterine cramps and systemic symptoms such as headache, dizziness, nausea, and vomiting. Especially prostaglandin F2 alpha (PGF2 alpha) causes uterine ischemia and pain by producing myometrial contractions and vasoconstriction. In one study, PGF2 alpha levels were four times higher in the endometrial samples of patients with primary dysmenorrhea compared to those of patients with eumenorrhea [2]. In addition to prostaglandins, increased levels of leukotrienes (LTs) and platelet activating factor (PAF) have been detected in the menstrual blood of dysmenorrhea patients. Moreover, no relation between the prostaglandins and the severity of dysmenorrhea has been found; however, a positive correlation has been detected between both LTs and PAF and severity of disease [3].

Blood cells play a role in inflammation. Platelets are activated in a variety of inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, arterial thrombosis, and asthma. Leukocytes play a major role in inflammatory processes and platelet–to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are considered as new markers of systemic inflammation [4,5]. The aim of this study was to investigate whether there is a relation between complete blood count parameters and PD during the menstrual cycle.

Materials and Methods

This study was performed in the Obstetrics and Gynecology Department at Dicle University Faculty of Medicine. This study was approved by the Ethics Committee of the University an informed consent was obtained from all participants in accordance with the Declaration of Helsinki before the study.

The participants of the study were selected from women admitted to the present gynecology clinic with symptoms of dysmenorrheal and for a routine control. The diagnostic criterion for primary dysmenorrhea was cyclic lower abdominal pain, beginning with or just before menstruation and abating within the first few days of menstruation and not related to any pathological condition. Patients who did not have regular menstrual cycles during the previous six months, required medication for any reason, had chronic diseases, smoked or drank alcohol, with diagnosed endometriosis, had identifiable pelvic pathology, or had experienced dysmenorrhea associated with an intrauterine device were excluded from this study. All study participants were informed about the study.

The study population consisted of 41 women with primary dysmenorrhea and a control group of 40 healthy women. Medical history of each participant was reviewed and all participants underwent a physical examination, including height and weight measurements, and pelvic ultrasonographic examination. Blood samples were obtained from all participants during each phase of one menstrual cycle: between the first and the fourth day of the cycle for the menstrual phase, between the ninth and the 12th day of the cycle for the follicular phase and between the 21st and the 23rd day of the cycle for the luteal phase according to ultrasonographic examination. During the menstrual phase, hormonal eval-

Revised manuscript accepted for publication January 10, 2013

uation (follicle stimulating hormone, luteinising hormone, prolactin, and thyroid stimulating hormone) was performed. Blood samples were drawn from the antecubital vein between 8:00 a.m. and 10:00 a.m. after an overnight fasting period. Blood samples were collected in tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA). All measurements were performed immediately after vein puncture to prevent in vitro platelet activation. The complete blood count was measured and hormone measurements were evaluated.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences version 15.0 (SPSS for Windows 15.0). Normality of continuous data was determined by Kolmogorov-Smirnov test. Parametric and non-parametric tests were conducted with independent Student t test, Mann-Whitney U test, and the Chi square test. Data were expressed as the mean ± standard deviation (SD). A two-tailed $p < 0.05$ was considered statistically significant for all comparisons.

Results

The mean age of the 41 patients with dysmenorrhea was 23.02 ± 3.43 years, and the mean age of the 40 patients in the control group was 23.76 ± 3.13 years ($p = 0.35$). Baseline demographic and laboratory characteristics of the patients in both groups are outlined in Table 1. Comparative analysis of the hematological parameters of study population and controls are displayed in Table 2. During all phases of the menstrual cycle, the mean platelet volume (MPV) was significantly lower in patients with PD (7.71 ± 1.17 vs 8.61 ± 1.79 ($p = 0.01$) in menstrual phase; 7.66 ± 0.81 vs 8.56 ± 1.75 ($p = 0.005$) in follicular phase; 7.75 ± 1.05 vs 8.53 ± 1.46 ($p = 0.01$) in luteal phase). No significant differences were found between the two groups for any of the other hematological parameters.

Table 1. — *Baseline characteristics.*

	Dysmenorrhea ($n = 41$)	Control ($n = 30$)	p value
Age (years)	23.02 ± 3.43	23.76 ± 3,13	NS
Age of menarche (years)	13.20 ± 1.20	12.90±1.30	NS
BMI (kg/m^2)	23.12 ± 4.76	22.84 ± 3.10	NS
FSH	5.93 ± 1.41	6.08 ±1.44	NS
LH	4.85 ± 2.05	5.49 ± 2.08	NS
PRL	13.72 ± 4.28	12.32 ± 4.35	NS
TSH	1.45 ± 0.65	1.70 ± 0.97	NS

Data are expressed as mean ± SD, NS (non-significant).
BMI: body mass index, FSH: follicle-stimulating hormone;
LH: luteinising hormone; PRL: prolactin.

Table 2. — *Hematological indices.*

	Dysmenorrhea ($n = 41$)	Control ($n = 30$)	p value
WBC 1	7.67 ± 1.46	6.88 ± 2.17	0.07
WBC 2	7.87 ± 2.05	7.82 ± 2.18	0.90
WBC 3	8.25 ± 2.00	7.48 ± 1.91	0.10
NEU 1	4.51 ± 1.21	3.90 ± 2.05	0.11
NEU 2	4.73 ± 1.69	4.30 ± 1.66	0.29
NEU 3	4.90 ± 1.92	4.34 ± 1.73	0.21
LYM 1	2.38 ± 0.57	2.24 ± 0.61	0.32
LYM 2	2.35 ± 0.56	2.37 ± 0.42	0.85
LYM 3	2.54 ± 0.66	2.40 ± 0.65	0.39
PLT 1	255.09 ± 52.53	243.76 ± 49.53	0.36
PLT 2	264.51 ± 52.59	262.46 ± 63.32	0.88
PLT 3	257.43 ± 53.66	246.30 ± 51.21	0.38
MPV 1	7.71 ± 1.17	8.61 ± 1.79	0.01
MPV 2	7.66 ± 0.81	8.56 ± 1.75	0.005
MPV 3	7.75 ± 1.05	8.53 ± 1.46	0.01
RDW 1	15.97 ± 1.75	15.92 ± 2.39	0.91
RDW 2	15.56 ± 2.04	15.66 ± 2.03	0.83
RDW 3	15.59 ± 2.02	15.61 ± 1.28	0.97
N/L 1	2.01 ± 0.82	1.88 ± 1.25	0.61
N/L 2	2.06 ± 0.74	1.84 ± 0.72	0.23
N/L 3	2.12 ± 1.22	1.94 ± 1.03	0.50
P/L 1	112.21 ± 33.08	116.25 ± 37.99	0.64
P/L 2	116.53 ± 27.43	114.10 ± 36.79	0.75
P/L 3	107.96 ± 35.15	108.88 ± 36.88	0.91

Data are expressed as mean ± SD
WBC: white blood cell; NEU: neutrophil; LYM: lymphocyte;
PLT: platelet; MPV: mean platelet volume;
RDW: red blood cell distribution width; N/L: neutrophil-to-lymphocyte ratio;
P/L: platelet-to-lymphocyte ratio; 1: values of menstrual phase;
2: values of follicular phase; 3: values of luteal phase.

Discussion

In the present study, when hematological parameters were evaluated for patients with PD, MPV was found to be significantly lower, compared to the control group, in all three phases of menstrual cycle. No significant differences were detected for other hematologic parameters. Platelets are essential blood cell components, which play a major role in hemostasis, inflammation and tissue regeneration. Platelets are activated in vascular and inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, arterial thrombosis, myocardial infarction, asthma, and transplant rejection [6-9]. MPV, which is an indicator of platelet activation and a component of the complete blood cell count (CBC), is inexpensive and is commonly used. MPV has been shown to increase in diseases associated with arterial thrombosis and in conditions associated with high cardiovascular risk, such as hypercholesterolemia, hypertension, and diabetes [8,10-13]. Larger platelets have more active substrates, metabolically and enzymatically, and more alpha granules [7,8]. They express and release more prothrombotic and vasoconstrictor factors, such as thromboxane A2, P-selectin, platelet-derived growth factor, and glycoprotein IIb-IIIa [14]. Vasoconstriction, adhesion, aggregation, and thrombosis occur in some diseases associated with high MPV due to the increased levels of prothrombotic and vasoconstrictor factors [15]. Unlike diseases with atherothrombosis, MPV has been reported to be lower in chronic inflammatory diseases. Kisacik *et al.* have shown that MPV is significantly lower in ankylosing spondylitis and rheumatoid arthritis patients with active disease as compared to con-

trols [16]. Similarly, Kapsoritakis *et al.* reported that MPV levels were significantly decreased in active inflammatory bowel disease, a finding that was well-correlated with the extent of the disease [7]. Gasparyan *et al.* found that MPV levels gradually increased in patients with rheumatoid arthritis, culminating in a significant difference at the end of the three months of anti-TNF therapy [17]. Decreased MPV levels have also been shown in inflammatory diseases in several other studies [18-20]. In addition to chronic inflammation, MPV was reported to be lower in acute inflammatory conditions, including acute attacks of chronic inflammatory diseases [20-22].

The cause of lower MPV in acute and chronic inflammatory conditions is still not entirely known. Increased production of acute phase reactants and pro-inflammatory cytokines due to inflammation may affect megakaryopoiesis resulting in the development of smaller platelets [20,23]. Another possible explanation for low MPV could be increased consumption of larger platelets at the inflammatory site [17]. Platelets that are structurally larger are more active and can release more pro-inflammatory and thrombotic agents [7,8]. Danese *et al.* speculated that reduced MPV could be due to the consumption or sequestration of large activated platelets in the intestinal vasculature of patients with Crohn's disease and ulcerative colitis [24]. It is possible that the increased demand at the inflammation site could result in increased consumption of larger platelets, leaving mostly platelets of smaller volume in systemic circulation.

Abnormal uterine activity with myometrial vasoconstriction and inflammation resulting from production of leukotrienes and prostaglandins are implicated in the etiology of primary dysmenorrheal [25]. PGF2 alpha is the most implicated agent in this process. Prostaglandin levels in the endometrial fluids of patients with dysmenorrhea were high and correlated with the severity of the pain [26]. Lundstrom demonstrated that intrauterine administration of PGF2 alpha during the secretory phase of the menstrual cycle increased uterine contractility [27]. However, some patients with dysmenorrhea do not derive any benefit from nonsteroidal anti-inflammatory medications, which act as anti-PG agents, suggesting the existence of other non-PG pathways in the etiology. High leukotriene (LT) infiltration has been observed in the endometriums of patients who did not respond to PG antagonists [3,28]. Rees *et al*. demonstrated increased LT levels in uterine tissue samples obtained after hysterectomies of patients who had dysmenorrhea [28]. Nigan *et al*. showed a close correlation between menstrual flow LT-C4/D4 levels and the severity of dysmenorrhea in patients who responded poorly to therapy with prostaglandin synthetase inhibitors [3]. Despite the many potential explanations, the pathogenesis of primary dysmenorrhea is still poorly understood. Recent evidence also links nitric oxide and vasopressin with dysmenorrhea pathogenesis [29,30].

In the present study, MPV levels of patients with PD were lower compared to the control group during all menstrual cycle phases. The authors believe that platelets may be involved in inflammatory process of PD. In addition to controlling thrombosis and hemostasis, platelets have role in inflammatory processes. The changes in megakaryopoiesis due to inflammation related to PD may have suppressed the size of the platelets. The fact that MPV was found to be low throughout the entire menstrual cycle suggests that the inflammation is not limited to the menstrual phase but continues as chronic inflammation in patients with PD. Alternatively, increased consumption of larger, metabolically active platelets in the uterine tissue in which inflammation occurs could explain the low MPV levels. The authors suggest that not only mediators released from the endometrial cells but also vasoactive substrates released from the large platelets in inflammation site might be causing uterine ischemia and pain via vasoconstriction in patients with PD.

The limitations of this study are that being relatively small number of study subjects and cross-sectional one center study design that limited the authors' ability to infer a casual association between MPV levels and PD, and may not be a real index of the general population.

Conclusion

In conclusion, the present findings imply that platelets may be involved in the inflammatory process for PD. Although the mechanism causing MPV change has not been fully explored, the authors suggest that low MPV values might indicate inflammation in patients with PD. On the other hand, low MPV in all phases of the menstrual cycle suggests that PD can be a chronic inflammatory process, which needs to be tested with larger scale studies.

References

[1] Durain D.: "Primary dysmenorrhea: assessment and management update". *J. Midwifery Womens Health*., 2004, *49*, 520.
[2] Lundstrom V., Green K.: "Endogenous levels of prostaglandin F2a and its main metabolites in plasma and endometrium of normal and dysmenorrheic women". *Am. J. Obstet. Gynecol*., 1978; *130*, 640.
[3] Nigam S., Benedetto C., Zonca M., Leo-Rossberg I., Lübbert H., Hammerstein J.: "Increased concentrations of eicosanoids and platelet activating factor in menstrual blood from women with primary dysmenorrhea". *Eicosanoids*, 1991, *4*, 137.
[4] Zahorec R.: "Ratio of neutrophil to lymphocyte counts: rapid and simple parameter of systemic inflammation and stress in critically ill". *Bratisl. Lek. Listy*., 2001, *102*, 5.
[5] McMillan D.C.: "Systemic inflammation, nutritional status and survival in patients with cancer". *Curr. Opin. Clin. Nutr. Metab. Care*, 2009, *12*, 223.
[6] Milovanovic M., Nilsson E., Järemo P.: "Relationships between platelets and inflammatory markers in rheumatoid arthritis". *Clin. Chim. Acta*., 2004, *343*, 237.
[7] Kapsoritakis A.N., Koukourakis M.I., Sfiridaki A., Potamianos S.P., Kosmadaki M.G., Koutroubakis I.E., *et al*.: "Mean platelet volume: a useful marker of inflammatory bowel disease activity". *Am. J. Gastroenterol*. 2001; *96*, 776.

[8] Endler G., Klimesch A., Sunder-Plassmann H., Schillinger M., Exner M., Mannhalter C., *et al*.: "Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease". *Br. J. Haematol*., 2002, *117*, 399.
[9] Kornerup K.N., Page C.P.: "The role of platelets in the pathophysiology of asthma". *Platelets*, 2007, *18*, 319.
[10] Muscari A., Puddu G.M., Cenni A., Silvestri M.G., Giuzio R., Rosati M., et al.: "Mean platelet volume (MPV) increase during acute nonlacunar ischemic strokes". Thromb. Res., 2009, 123, 587.
[11] Papanas N., Symeonidis G., Maltezos E., Mavridis G., Karavageli E., Vosnakidis T., et al.: "Mean platelet volume in patients with type 2 diabetes mellitus". *Platelets*, 2004, *15*, 475.
[12] Nadar S., Blann A.D., Lip G.Y.: "Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipinebased antihypertensive therapy. *Ann. Med*. 2004, *36*, 552.
[13] Pathansali R., Smith N., Bath P.: "Altered megakaryocyte–platelet haemostatic axis in hypercholesterolaemia". *Platelets*, 2001, *12*, 292.
[14] Lancé M.D., Sloep M., Henskens Y.M., Marcus M.A.: "Mean platelet volume as a diagnostic marker for cardiovascular disease. Drawbacks of preanalytical conditions and measuring techniques". *Clin. Appl. Thromb. Hemost*., 2012, *18*, 561. doi: 10.1177/1076029612458147. Epub 2012 Aug 30
[15] Tsiara S., Elisaf M., Jagroop I.A., Mikhailidis D.P.: "Platelets as predictors of vascular risk: is there a practical index of platelet activity?" *Clin. Appl. Thromb. Hemost*., 2003, *9*, 177.
[16] Kisacik B., Tufan A., Kalyoncu U., Karadag O., Akdogan A., Ozturk M.A., *et al*.: "Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis". *Joint Bone Spine*, 2008, *75*, 291.
[17] Gasparyan A.Y., Sandoo A., Stavropoulos-Kalinoglou A., Kitas G.D.: "Mean platelet volume in patients with rheumatoid arthritis: the effect of anti-TNF-α therapy". *Rheumatol. Int*., 2010, *30*, 1125.
[18] Jaremo P., Sandberg-Gertzen H.: "Platelet density and size in inflammatory bowel disease". *Thromb. Haemost*., 1996, *75*, 560.
[19] Yüksel O., Helvaci K., Basar O., Köklü S., Caner S., Helvaci N., *et al*.: "An overlooked indicator of disease activity in ulcerative colitis: mean platelet volume". *Platelets*, 2009, *20*, 277.
[20] Makay B., Turkyilmaz Z., Unsal E.: "Mean platelet volume in children with familial Mediterranean fever". *Clin. Rheumatol*., 2009, *28*, 975.
[21] Albayrak Y., Albayrak A., Albayrak F., Yildirim R., Aylu B., Uyanik A., *et al*.: "Mean platelet volume: a new predictor in confirming acute appendicitis diagnosis". *Clin. Appl. Thromb. Hemost*., 2011; *17*, 362.
[22] Beyazit Y., Sayilir A., Torun S., Suvak B., Yesil Y., Purnak T., *et al*.: "Mean platelet volume as an indicator of disease severity in patients with acute pancreatitis". *Clin. Res. Hepatol. Gastroenterol*., 2012, *36*, 162.
[23] Bath P.M., Butterworth R.J.: "Platelet size: measurement, physiology and vascular disease". *Blood Coagul. Fibrinolysis*, 1996, *7*, 157.
[24] Danese S., Motte Cd Cde L., Fiocchi C.: "Platelets in inflammatory bowel disease: clinical, pathogenic, and therapeutic implications". *Am. J. Gastroenterol*., 2004, *99*, 938.
[25] Harel Z.: "A contemporary approach to dysmenorrhea in adolescents. *Paediatr. Drugs*, 2002, *4*, 797.
[26] Hacker N.F., Moore J.G., eds.: "Essentials of Obstetrics and Gynecology". In: *Dysmenorrhea and premenstrual syndrome*, 3rd ed. Philadelphia, WB Saunders, 1998, 386.
[27] Lundstrom V.: "The myometrial response to intra-uterine administration of PGF2alpha and PGE2 in dysmenorrheic women". *Acta Obstet. Gynecol. Scand*., 1977, *56*, 167.
[28] Rees M.C., DiMarzo V., Tippins J.R., Morris H.R., Turnbull A.C.: "Leukotriene release by endometrium and myometrium throughout the menstrual cycle in dysmenorrhoea and menorrhagia". *J. Endocrinol*., 1987, *113*, 291.
[29] Moya R.A., Moisa C.F., Morales F., Wynter H., Ali A., Narancio E.: "Transdermal glyceryl trinitrate in the management of primary dysmenorrhea". *Int. J. Gynaecol. Obstet*., 2000, *69*, 113.
[30] French L.: "Dysmenorrhea". *Am. Fam. Physician*, 2005, *71*, 285.

Address reprint requests to:
H. E. SOYDINC, M.D.
Dicle University, School of Medicine,
Department of Gynecology and Obstetrics,
21280, Diyarbakir (Turkey)
e-mail: endersoydinc@hotmail.com