Effect of combined oral contraceptive use on platelet volume in women at reproductive age

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Summary

Investigation: Combined oral contraceptives use is associated with an increased risk of developing venous and arterial thromboembolic events. Platelet size, measured as mean platelet volume (MPV), is associated with platelet reactivity. *Methods:* Ninety-five women using oral contraceptives for contraception were investigated retrospectively. The patients' blood pressure, pulse and hematological values at application and at the sixth month were evaluated retrospectively. *Results:* There was no difference between the values of blood pressure (systolic and diastolic), pulse, hematological values (which contain leukocytes, platelets and mean platelet volume) at application and at the sixth month. *Conclusion:* We determined that using oral contraceptives for contraception did not change MPV values in young women.

Key words: Combined oral contraceptives; Mean platelet volume.

Introduction

Combined oral contraceptives (COC) represent the most extensively used method for birth control with about 100 million users worldwide [1]. However, COC use is associated with an increased risk of developing venous and arterial thromboembolic events.

Epidemiological studies indicate that COC use increases the absolute risk of venous thrombosis (VT) [2] and all cardiovascular arterial diseases such as myocardial infarction and ischemic stroke [3]. Platelet size, measured as mean platelet volume (MPV), is associated with platelet reactivity. MPV increases in acute myocardial infarction, and this has been identified as an independent risk factor for future myocardial infarction and stroke. An increasing MPV was identified as a predictor for venous thromboembolism (VTE). The present findings support the concept that platelet reactivity is important in the pathogenesis of VTE [4]. High MPV is associated with a variety of established risk factors, cardio- and cerebrovascular disorders, and low-grade inflammatory conditions prone to arterial and venous thromboses [5].

However, MPV values have never been studied in reproductive age women who were using oral contraceptives. Therefore, we aimed to investigate the effect of oral contraceptive use on MPV in reproductive age women.

Material and Method

Ninety-five reproductive age women who were admitted to the university hospital or were referred to their family physician in Konuralp/Duzce region from June 2010 to December 2010 and used oral contraceptives were investigated retrospectively. Exclusion criteria were known diseases that could affect MPV; strictly speaking, polycystic ovary syndrome, bleeding disorders, genetic disorders (factor V Leiden, protein C, S and antithrombin deficiency, antiphospholipid syndrome) history of venous thromboembolism, pregnancy, chronic liver and kidney diseases, any kind of malignancy, trauma, chronic immobilization, surgery and antiplatelet use.

Clinical and demographic data before COC administration and at the sixth month visit including blood pressure, pulse, and hematological values were obtained from medical files and recorded. These data were evaluated retrospectively. The ethical committee of the medical faculty of Duzce University approved the study protocol.

Biochemical measurements: Blood samples were drawn after a fasting period of 12 h. Glucose, creatinine, alanine aminotransferase and lipid profile was determined by standard methods. We measured MPV and platelet count in a blood sample collected in citrate (1:4 v/v) in order to avoid platelet swelling induced by EDTA. A Cell-Dyn 3500 (Abbot) was used for whole blood counts. MPV (fL) was measured directly. The expected values for MPV in our laboratory ranged from 7.0-11 fL.

Statistical analysis: Statistical analyses were performed using the statistical package SPSS 13.0 for Windows. Normally distributed continuous variables among groups were compared with the paired t-test. The chi-square test was used to compare categorical variables. MPV values were compared with the Student's t-test in smokers and non-smokers. A p value < 0.05 was considered statistically significant.

Results

The mean age of the individuals was 29 ± 6 (minimum: 16, maximum: 45) and mean body mass index (BMI) was 25 ± 3 (minimum: 19, maximum: 29). Mean follow-up time was 6 ± 1.5 months. No women had any episode of thromboembolism during the study period. Twenty-nine women (31%) were smokers. Forty of them (42%) were using 0.15 mg levonorgestrel and 0.03 mg ethinylestradiol, 50 (53%) were using 3 mg drospirenone and 0.03 mg ethinylestradiol, and five (5%) were using 0.1 mg lev-

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Table 1. — *General characteristics of individuals*.

Age (years)	29 ± 3
Follow up time (months)	6 ± 1.5
BMI (kg/m^2)	25 ± 3
Fasting plasma glucose (mg/dl)	92 ± 13
Total cholesterol (mg/dl)	167 ± 32
HDL (mg/dl)	49 ± 11
Triglyceride (mg/dl)	95 ± 54
Creatinine (mg/dl)	07 ± 0.1
AST (IU/l)	21 ± 10
BUN (mg/dl)	19 ± 26

BMI: body mass index.

Table 2. — *The values before and after COC use*.

	Before	Follow-up time	*p* value
Systolic BP (mmHg)	113 ± 13	113 ± 12	0.45
Diastolic BP (mmHg)	74 ± 6	74 ± 7	0.90
Heart rate (beat/minute)	73 ± 6	72 ± 6	0.58
Hemoglobin (g/dl)	12.6 ± 1.3	12.6 ± 1.2	0.81
White Blood Cell (n/ml)	7.7 ± 2	7.4 ± 2	0.36
Platelet counts (10^9)	264 ± 65	268 ± 71	0.63
Mean platelet volume (fl)	8.7 ± 1.6	8.8 ± 1.9	0.75

BP: Blood pressure.

onorgestrel and 0.02 mg ethinylestradiol. The main characteristics of the study population are reported in Table 1. There was no difference between the values of blood pressure (systolic and diastolic) (p = 0.45 and p = 0.90, respectively), pulse, hematological values (which contain leukocytes, platelets and mean platelet volume) (p = 0.36, p = 0.63, p = 0.75, respectively) at application and at the sixth month (Table 2). Mean MPV did not differ between smokers and non smokers.

Discussion

We determined that using oral contraceptives for contraception did not change MPV values in reproductive age women. Also MPV did not significantly differ in smokers and their non-smoker counterparts. This is concordant with the data published by Butsckiewich *et al*. They showed that smoking had no effect on mean platelet volume, percentage of large platelets, concentration of thrombopoietin, absolute count of reticulated platelet and concentration of beta1-thromboglobulin in women [6].

Mean platelet volume, introduced as a new method for the assessment of platelet activation [7], is a platelet function index that reflects platelet production rate and stimulation. Increased platelet volume is associated with increased platelet reactivity, shortened bleeding time, [8] and increased platelet aggregation ex vivo [9]. Large platelets have higher thrombotic potential [10] and express higher levels of P-selectin [11] and glycoprotein IIb-IIIa [12] than small platelets. It has been reported that elevated values of MPV are associated with cardiovascular disease [13]. It also increases in acute myocardial infarction, acute ischemic stroke and venous thromboembolism [4, 14, 15].

Among current COC users, there was a 2.5 relative increased risk of adverse cardiovascular events, including cardiovascular death, nonfatal MI, and stroke. The increase in cardiovascular deaths and nonfatal MI and stroke in current users was believed to be associated with the prothrombotic effects, and seven of ten adverse cardiovascular events occurred in current cigarette smokers [16]. It has been demonstrated that the risk of VT is the highest in the first year of pill use [17, 18], particularly during the first three months of COC use [19]. Stopping COCs was associated with a decline in the risk for adverse cardiovascular events, suggestive of reversal of the COC prothrombotic effects with cessation of use; however, other mechanisms such as an antiatherosclerotic effect could also be contributory [20].

The identification of MPV as a risk factor for VTE suggests that platelet size may be a common risk factor for both arterial and venous thrombosis [4]. The results of the present study however suggest that thromboembolic risk in COC users could not be screened through MPV measurement. This may be due to a potential mechanism that influences the increased VTE risk in COC users by a non-platelet coagulation cascade.

In conclusion it was determined that in reproductive age women use of oral contraceptives had no negative impact on MPV values. However, prospective controlled larger scale studies are needed to define further the role of COC on platelet indices in women at reproductive age.

References

[1] Report of a WHO Scientific Group. Cardiovascular disease and steroid hormone contraception. World Health Organ Tech Rep Ser 1998, 877: i-vii, 1.

[2] Tchaikovski S.N., Rosing J.: "Mechanisms of estrogen-induced venous thromboembolism". *Thromb. Res*., 2010, 126, 5.

[3] Baillargeon J.P., McClish D.K., Essah P.A., Nestler J.E.: "Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis". *J. Clin. Endocrinol. Metab.,* 2005, *90,* 3863.

[4] Braekkan S.K., Mathiesen E.B., Njølstad I., Wilsgaard T., Størmer J., Hansen J.B.: "Mean platelet volume is a risk factor for venous thromboembolism: the Tromsø Study, Tromsø, Norway". *Thromb. Haemost.,* 2010, *8*, 157.

[5] Gasparyan A.Y., Ayvazyan L., Mikhailidis D.P., Kitas G.D.: "Mean platelet volume: a link between thrombosis and inflammation?". *Curr. Pharm. Des*., 2011, 17, 47.

[6] Butkiewicz A.M., Kemona-Chetnik I., Dymicka-Piekarska V., Matowicka-Karna J., Kemona H., Radziwon P.: "Does smoking affect thrombocytopoiesis and platelet activation in women and men?". *Adv. Med. Sci.,* 2006, *51,* 123.

[7] Uchiyama S., Takeuchi M., Osawa M., Kobayashi I., Maruyama S., Aosaki M., Hirosawa K.: "Platelet function tests in thrombotic cerebrovascular disorders". *Stroke,* 1983, *14,* 511.

[8] Martin J.F., Trowbridge E.A., Salmon G., Plumb J.: "The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration". *Thromb. Res.,* 1983, *32,* 443.

[9] Sharp D.S., Bath P.M.W., Martin J.F., Beswick A.D., Sweetnam P.M.: "Platelet and erythrocyte volume and count: epidemiological predictors of impedance measured ADP-induced platelet aggregation in whole blood". *Platelets*, 1994, *5*, 252.

[10] Karpatkin S., Khan Q., Freedman M.: "Heterogeneity of platelet function. Correlation with platelet volume" (Review). *Am. J. Med.,* 1978, *64*, 542.

[11] Breimo E.S., Østerud B.: "Studies of biological functions in blood cells from individuals with large platelets". *Platelets,* 2003, *14*, 413.
[12] Pathansali R., Smith N.M., Bath P.M.: "Prothrombotic megakaryocyte and platelet changes in hypertension are reversed following treatment: a pilot study". *Platelets*, 2001, *12*, 144.
[13] Pizzulli L., Yang A., Martin J.F., Lüderitz B.: "Changes in platelet size and count in unstable angina compared to stable angina or non-cardiac chest pain". *Eur. Heart J.,* 1998, *19,* 80.
[14] Bath P.M., Butterworth R.J.: "Platelet size: measurement, physiology and vascular disease". *Blood Coagul Fibrinolysis.,* 1996, *7*, 157.
[15] Jagroop I.A., Mikhailidis D.P.: "Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease". *Br. J. Haematol*., 2003, *120*, 169.
[16] Stampfer M.J., Willett W.C., Colditz G.A., Speizer F.E., Hennekens C.H.: "A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases". *N. Engl. J. Med.,* 1988, *319*, 1313.
[17] Herings R.M., Urquhart J., Leufkens H.G.: "Venous thromboembolism among new users of different oral contraceptives". *Lancet,* 1999, *354,* 127.
[18] Bloemenkamp K.W., Rosendaal F.R., Helmerhorst F.M., Vandenbroucke J.P.: "Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects". *Arch. Intern. Med*., 2000, *160,* 49.
[19] van Hylckama Vlieg A., Helmerhorst F.M., Vandenbroucke J.P., Doggen C.J., Rosendaal F.R.: "The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study". *BMJ,* 2009, *339,* b2921.
[20] Shufelt C.L., Bairey Merz C.N.: "Contraceptive hormone use and cardiovascular disease". *J. Am. Coll. Cardiol.,* 2009, *53,* 221.

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