Original Article

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Mean Platelet Volume in Women with Gestational Diabetes

Gestasyonel Diyabetli Kadınlarda Ortalama Trombosit Hacmi

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Abstract

Purpose: Mean platelet volume (MPV) is an indicator of platelet activation which plays an important role in the pathogenesis of atherosclerosis. The purpose of this study was to compare MPV values in patients with previous gestational diabetes (pGDM), who have different degrees of carbohydrate intolerance with that in women without pGDM; and to retrospectively analyze MPV in these women during pregnancy.
Material and Method: One hundred and five consecutive women with gestational diabetes mellitus (GDM) and 40 women with negative screening for GDM were studied.
Results: There was no statistically significant difference in MPV between women with pGDM and health controls. Although not significant, women with pGDM developing type 2 diabetes had elevated levels of MPV compared to their normoglycemic counterparts (p=0.092). MPV was positively correlated with fasting glucose levels (r=0.215, p=0.009). During pregnancy, the mean platelet volume was significantly higher in women with GDM than in healthy pregnant controls (p<0.05).
Discussion: Our results suggest that alterations in MPV levels are associated with diabetic state rather than underlying insulin resistance.
Keywords: Gestational diabetes, mean platelet volume, platelets, pregnancy, type 2 diabetes

Öz

Amaç: Ortalama trombosit hacmi (MPV) ateroskleroz patogenezinde önemli bir rol oynayan bir trombosit aktivasyon belirtecidir. Bu çalışmanın amacı farklı düzeylerde karbonhidrat intoleransı saptanmış gestasyonel diyabet (GDM) öyküsü olan kadınlarda ve GDM negatif kontrol grubunda MPV düzeylerini çalışmak; ve bu kadınlardaki gebelik dönemindeki MPV'yi retrospektif olarak analiz etmektir.
Gereç ve Yöntem: GDM tanısı almış 105 kadın hasta ve 40 tarama negatif kontrol çalışmaya dahil edildi.
MPV düzeyleri GDM öyküsü olan kadınlarda normal gebelik öyküsü olan kadınlardan farklı değildi. Anlamlı olmamakla birlikte tip 2 diyabet gelişen GDM öyküsü olan kadınlarda normoglisemik hastalara göre daha yüksek MPV düzeyleri bulundu (p=0,092). MPV açlık glikozu ile pozitif yönde koreleydi (r=0,215, p=0,009).
Bulgular: Gebelik döneminde MPV gestasyonel diyabetli kadınlarda sağlıklı gebe kontrollerden anlamlı olarak daha yüksek bulundu (p<0,05).
Tartışma: Sonuçlarımız ortalama trombosit hacminin altta yatan insülin direncinden ziyade diyabetik durum ile ilişkili olduğunu göstermektedir.
Anahtar kelimeler: Gestasyonel diyabet, ortalama trombosit hacmi, trombosit, gebelik, tip 2 diyabet

Introduction

Gestational diabetes mellitus (GDM) is a type of diabetes that affects women during pregnancy (1). Approximately 3-10% of all pregnancies are complicated with GDM (2). In pregnancy, insulin resistance increases due to rising concentrations of insulin antagonists, such as cortisol, prolactin, leptin and human placental antigen (3,4). Along with insulin resistance, beta cell dysfunction may be involved in the pathogenesis of gestational diabetes. Insulin resistance during pregnancy may extend to postpregnancy period (5). Women with a history of GDM have a higher risk of developing type 2 diabetes or altered glucose metabolism (1). Several studies demonstrated impaired insulin sensitivity and beta cell dysfunction among normo-glycaemic women with a history of GDM (5,6,7). Since insulin resistance is a well-known atherosclerotic risk factor, women with previous GDM (pGDM) may have increased risk for cardiovascular disease. In addition to insulin resistance, pGDM is also associated with endothelial dysfunction which is an early indicator of atherosclerosis (8,9).
Platelets play a crucial role in the pathogenesis of atherosclerosis (10,11). Larger platelets are more active than smaller platelets (12). They have higher levels of procoagulatory intracellular proteins like thromboxane A2 and surface proteins like p-selectin and glycoprotein IIIa (11,13,14). There is a wide range of indices which have been used to assess the platelet function. Quantification of mean platelet volume (MPV) is one of them and is a simple method that determines the platelet size (15). Increased MPV has been shown in patients with known atherosclerotic risk factors, such as diabetes mellitus, obesity, impaired fasting glucose

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(IFG) and hypertension (16,17,18,19). The purpose of this study was to compare MPV values in patients with pGDM who have different degrees of carbohydrate intolerance with that in women without pGDM who have normal glucose tolerance (NGT), and to retrospectively analyze MPV in those women during pregnancy.

Materials and Methods

One hundred and five consecutive women with GDM and 40 women with healthy pregnancy were included in this study. Women were screened for GDM between 24 and 28 weeks of gestation with a 50-g oral glucose challenge test using 1-h plasma glucose during their index pregnancies. Women with a value of ≥130 mg/dL underwent 100-g oral glucose tolerance test (OGTT) and plasma glucose values for diagnosis of GDM were based on the guidelines of the American Diabetes Association (ADA) (20). Control group was composed of age-matched healthy hospital staff who had a 1-hour plasma glucose level of less than 130 mg/dL on 50-g glucose challenge test between 24-28 weeks of gestation during their index pregnancies.

Women with type 1 diabetes, type 2 diabetes and abnormal glucose tolerance before pregnancy, moderate and severe anaemia (defined as <10 gr/dL), thrombocytopenia (defined as $<150x10^9$/L), haemoglobinopathy, chronic disease, preeclampsia, and alcohol consumption were excluded. Pregnant women in high-risk group including severe obesity, prior history of GDM or delivery of large-for-gestational-age-infant, diagnosis of polycystic ovary syndrome, and strong family history of type 2 diabetes were excluded from the study because they were screened at first antenatal visit, before 24-28 weeks of gestation. Women who had early (before 36 weeks of gestation) or late delivery (after 42 weeks of gestation) were excluded because MPV values before delivery should be obtained between 36-42 weeks of gestation according to the study design.

The study was approved by the Local Ethics Committee of Dokuz Eylül University. Informed consent was obtained from all subjects. Prenatal records of patients with GDM and control subjects were retrospectively collected from our computerized database (Genesis Plus, İzmir, Turkey). Data regarding prepregnancy body weight, weight gain during pregnancy, maternal and foetal complications, 50-g glucose challenge test, 100-g OGTT and complete blood count during 24-28 weeks and 36-42 weeks of gestation were recorded. MPV levels and platelet counts between 24-28 weeks of gestation, at the time of screening for GDM, were recorded as MPV and platelet count at the time of the screening of GDM and those between 36-42 weeks of gestation, at the time of the last antenatal visit before delivery, were recorded as MPV and platelet count late in the third trimester.

At the time of enrolment, data about detailed medical history of subjects were recorded. Blood pressure was obtained. Height (m), weight (kg) and waist circumference (cm) were measured under fasting conditions with subjects in light clothes, without shoes and in upright position. Waist circumference was measured at the highest point of the iliac crest at minimal respiration. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Blood pressure was measured using a sphygmomanometer in sitting position after 5 minute rest. Subjects having a blood pressure higher than 140 mmHg for systolic and 90 mmHg for diastolic or patients under antihypertensive medication at the time of enrolment were defined as hypertensive. Smoking habits and family history of diabetes were questioned.

All women with pGDM and healthy controls underwent a 75-g oral glucose tolerance test. Impaired glucose tolerance (IGT), IFG and type 2 diabetes were defined according to the ADA guidelines (21). Fasting blood samples for haematological parameters, total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, insulin and fibrinogen levels were obtained in the morning from a forearm vein with minimal trauma. Venous samples for complete blood count were collected into 7.5% tripotassium EDTA tubes and analyzed within 2 hours of venipuncture. An automatic cell analyzer (LH 780, Beckman Coulter, Krefeld, Germany) was used for the automated differential blood cell counting. All blood samples were analyzed by the same analyzer. Glucose levels on OGTT were measured by a calorimetric method with Roche/Hitachi D/P Modular System Autoanalyzer (Roche Diagnostics, Basel, Switzerland). 100-g 3 hour OGTT glucose area was calculated by the trapezoid method. Thus, the total area under the 3-h OGTT curve was calculated by: OGTTAUC = ½ x (Glucose t_0 + Glucose t_3) + Glucose t_1 + Glucose t_2 (t=time). Insulin levels were measured by a chemiluminescent method (Roche Diagnostics, Mannheim, Germany) using an automatic immunoanalyzer. Homeostasis model assessment (HOMA) score was calculated as fasting serum insulin (μU/mL) x fasting plasma glucose (mmol/L)/22.5. Total cholesterol, triglyceride, and HDL cholesterol were measured by Roche/Hitachi D/P Modular System Autoanalyzer (Roche Diagnostics, Basel, Switzerland). LDL cholesterol was calculated by the Friedewald's equation method (22). Plasma fibrinogen was analyzed by the Clauss method (23).

Sample size determination used a significance level of 0.05 for a two-tailed test with 80% power. The sample size was calculated using the Power and Precision software. Data were analyzed with the Statistical Package of Social Science (SPSS), software version 11.0 for Windows. Continuous variables were presented as mean ± standard deviation and categorical variables as frequency and percentage. Variable distributions were assessed by the Kolmogorov-Smirnov normality test. According to the variable distribution, Student t-test and the Mann-Whitney U test were applied for comparison of groups. Nominal variables were assessed by a chi-square test. The relationships between variables were assessed by Pearson's correlation analysis. Statistical significance was defined as two-sided p value of <0.05.

Results

Baseline clinical characteristics and laboratory results of study population are shown in Table 1. The mean age and postpartum duration of the study groups were similar. More people had positive family history for type 2 diabetes in the GDM group compared to the control group. Women with GDM were found to have higher weight, waist circumference and BMI at the time of

enrolment. Patients with GDM had increased levels of total and LDL cholesterol, triglyceride, fasting and post-load glucose, insulin, HOMA score, and fibrinogen and decreased HDL cholesterol level when compared to those in the control group. MPV obtained at the time of enrolment was not significantly different between women with GDM and with normal pregnancy. During the course of pregnancy, platelet count decreased and MPV increased gradually from 24-28 weeks of gestation to 36-42 weeks in women with GDM. After delivery, MPV was found to be decreased below the values seen during pregnancy (Figure 1). MPV at the time of screening for GDM and MPV late in the third trimester were found to be higher in women with GDM (p=0.039 and p=0.036, respectively).

Table 2 shows the characteristics of patients in the pGDM group with newly diagnosed type 2 diabetes, IFG/IGT and NGT. Among patients with pGDM, 13 patients were diagnosed with type 2 diabetes, 48 patients with IFG/IGT, whereas 44 patients were found to have NGT at the time of enrolment. In the control group, there were no subjects with any degree of glucose intolerance. When patients in the pGDM group who had newly diagnosed type 2 diabetes and those who had NGT were compared, MPV was tended to be increased in patients with type 2 diabetes (p=0.092). When the patients in the pGDM group with IFG/IGT and the patients with NGT were compared, there was no difference in current MPV.

In correlation analysis, the current MPV was found to be positively correlated with fasting glucose levels at the time of enrolment (r=0.215, p=0.009). The current MPV was also positively correlated with MPV at the time of screening (r=0.615, p<0.001) and MPV late in the third trimester (r=0.404, p<0.001).

Discussion

In this study, MPV was not significantly different between women with pGDM and women with previous normal pregnancies. MPV values were tended to be increased in women with pGDM who had type 2 diabetes compared to those who had NGT. MPV was found to be positively correlated with fasting glucose levels. When retrospectively analyzed, women with GDM were found to have higher MPV values at the time of screening for GDM and late in the third trimester than women without GDM.

GDM represents insulin resistance during pregnancy that may extend beyond postpartum period. Insulin resistance is associated with some alterations in platelet activity in favour of thrombosis (24,25). MPV has been found to be significantly increased in insulin

Table 1. Baseline clinical characteristics and laboratory results of patients with gestational diabetes mellitus and healthy controls

	GDM (n=105)	Control (n=40)	p
Age (years)	33.41±4.94	33.32±3.82	0.904
Smoking (n, %)	19 (18.1%)	11 (27.5%)	0.252
Hypertension (n, %)	6 (5.7%)	0	0.188
Postpartum duration (months)	35.48±20.20	40.02±20.76	0.232
Family history of type 2 diabetes (n, %)	50 (47.6%)	9 (22.5%)	0.008
Weight (kg)	72.52±12.98	62.31±9.95	<0.001
Waist (cm)	91.99±12.23	82.82±11.96	<0.001
BMI (kg/m^2)	27.74±4.99	23.63±3.52	<0.001
Total cholesterol (mg/dL)	196.53±41.44	167.90±32.82	<0.001
Triglyceride (mg/dL)	122.10±67.87	78.45±33.04	<0.001
HDL cholesterol (mg/dL)	50.50±14.99	59.15±15.09	0.002
LDL cholesterol (mg/dL)	121.62±34.78	93.06±32.60	<0.001
$OGTT_{t0}$ (mg/dL)	104.06±21.66	78.12±8.13	<0.001
$OGTT_{t2}$ (mg/dL)	134.32±51.70	84.0±13.50	<0.001
Insulin (µU/mL)	7.80±5.84	5.55±3.12	0.003
HOMA	2.03±1.52	1.07±0.63	<0.001
Fibrinogen (g/L)	4.18±1.10	3.46±0.73	0.001
Current MPV (fL)	8.76±1.08	8.56±1.09	0.320
Current PLT (x 10^9/L)	278.39±63.60	276.15±57.35	0.846
MPV late in 3rd trimester (fL)	9.59±1.34	8.95±1.98	0.036
PLT at late in 3rd trimester (x10^9/L)	210.42±56.75	217.97±61.85	0.508
MPV at the time of screening (fL)	8.66±1.15	8.27±0.92	0.039
PLT at the time of screening (x10^9/L)	253.77±69.43	253.52± 60.43	0.984

Data were expressed as mean ± standard deviation, GDM: Gestational diabetes mellitus, pGDM: Previous gestational diabetes mellitus, BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein, OGTT: Oral glucose tolerance test, HOMA: Homeostasis model assessment, MPV: Mean platelet volume, PLT: Platelet count

resistant states such as diabetes, IFG, obesity and metabolic syndrome (16,17,18,26). Platelet size, which can be measured as MPV, determines platelet function. Large platelets contain denser granules, thus, they are enzimatically and metabolically more active in the pathogenesis of thrombosis and atherosclerosis than small platelets (11).

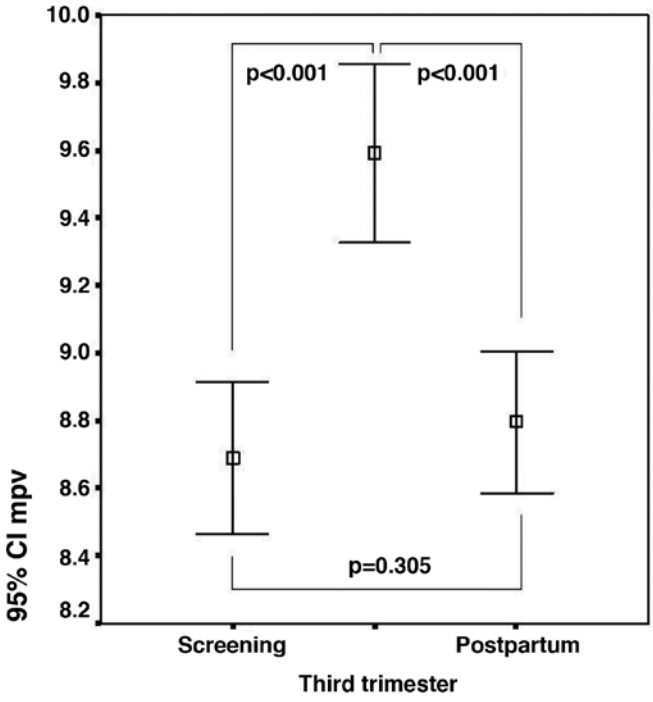

Figure 1. The alteration of mean platelet volume during pregnancy and postpartum period in women with gestational diabetes mellitus
MPV: Mean platelet volume

In the present study, patients with pGDM were found to have similar MPV values with healthy controls while they had increased insulin resistance along with more atherogenic lipid profile and increased levels of plasma fibrinogen. MPV was found to be higher in two diabetic states. First, MPV tended to be higher in women with pGDM who had type 2 diabetes compared to women with pGDM who had NGT. MPV was positively correlated with fasting glucose level as well. Second, during pregnancy, women with GDM whose blood glucose levels were simply increased had significantly higher MPV than women without GDM. However, MPV values in women with IFG/IGT were similar with those in women with NGT in spite of the significant difference in insulin resistance. These findings suggest that alterations in MPV values were associated with a diabetic state rather than an underlying insulin resistance. The correlation between fasting blood glucose and MPV supports such a relationship as well. The insignificant difference in the current MPV in women with pGDM who had type 2 diabetes may be due to the small number of patients with diabetes in our study population. In concordance with our results, it has been reported that MPV levels obtained in the last trimester were significantly higher in women with GDM compared to healthy pregnant controls (27). Saigo et al. (28) demonstrated a correlation between blood glucose level and platelet volume in diabetic patients. In another study, the mechanism of increased platelet volume in diabetic patients was proposed to be isosmotic swelling due to raised level of blood glucose or glucose metabolites (29). In contrast to these studies, few

Table 2. The comparison of patients with previous gestational diabetes mellitus with newly diagnosed type 2 diabetes, impaired fasting glucose/impaired glucose tolerance and normal glucose tolerance (NGT)

	Diabetes (n=13)	IFG-IGT (n=48)	NGT (n=44)	p†	p‡
Age (years)	34.23±6.04	33.06±5.02	33.56±4.58	0.672	0.616
Weight (kg)	72.38±11.85	78.31±13.13	66.25±10.11	0.070	<0.001
BMI (kg/m^2)	28.16±4.39	29.91±5.32	25.25±3.49	0.016	<0.001
Waist (cm)	93.15±12.10	97.31±11.49	85.84±10.28	0.035	<0.001
Prepregnancy weight (kg)	66.69±9.59	73.77±11.43	64.22±11.52	0.486	<0.001
Prepregnancy BMI (kg/m^2)	25.95±3.67	28.17±4.52	24.47±4.00	0.237	<0.001
$OGTT_{t0}$ (mg/dL)	105.30±35.91	99.50±16.39	87.02±12.78	0.095	<0.001
$OGTT_{t1}$ (mg/dL)	233.75±37.70	219.97±25.98	207.88±28.85	0.014	0.040
$OGTT_{t2}$ (mg/dL)	193.66±58.66	188.93±32.67	184.33±27.76	0.603	0.479
$OGTT_{t3}$ (mg/dL)	133.16±58.62	130.55±40.87	129.50±39.75	0.802	0.902
AUC_{OGTT}	545.04±127.17	524.08±68.04	500.60±56.84	0.261	0.083
Insulin (µU/mL)	6.67±3.72	9.66±5.89	6.06±5.78	0.724	0.004
HOMA	2.33±1.50	2.56±1.52	1.34±1.28	0.023	<0.001
Fibrinogen (g/L)	4.94±1.17	4.23±1.11	3.87±0.95	0.002	0.118
MPV (fL)	9.28±1.50	8.69±1.07	8.69±0.93	0.092	0.994

†Type 2 diabetes group vs. NGT group ‡IFG/ IGT group vs. NGT group, Data were expressed as mean ± SD, pGDM: Previous gestational diabetes mellitus, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, NGT: Normal glucose tolerance, BMI: Body mass index, OGTT: Oral glucose tolerance test, AUC: Area under curve, HOMA: Homeostasis model assessment, MPV: Mean platelet volume, PLT: Platelet count

studies failed to show any relationship between MPV and blood glucose level (30,31).

An inverse relationship has been shown between platelet count and MPV in healthy subjects (32). Similarly, we found that MPV increased and platelet count decreased significantly throughout the pregnancy. This may be attributed to decreased platelet concentration secondary to increased plasma volume and accelerated platelet production in response to platelet destruction due to increased cardiac output and following endothelial damage during the pregnancy (33). By accelerated platelet production, young platelets with higher volume increase in circulation throughout the pregnancy (34).

Study Limitations

There are some limitations of this study. First, women who had high risk for GDM were not included due to the study design as they were screened at first antenatal visit. Second, the sample size for patients in pGDM group who had newly diagnosed type 2 diabetes may not be large enough to detect statistical significance of differences. Third, MPV values during index pregnancy were recorded retrospectively.

Conclusion

MPV was not statistically different between women with pGDM and women with previous healthy pregnancies. On the other hand, MPV was positively correlated with fasting glucose. Besides, women in the pGDM group who had newly diagnosed type 2 diabetes tended to have higher MPV when compared to those who had NGT. During pregnancy, MPV at the time of screening of GDM and MPV late in the third trimester were significantly higher in women with GDM. Our results revealed that alterations in MPV values were associated with a diabetic state rather than an underlying insulin resistance.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Dokuz Eylül University, Informed consent was obtained from all subjects, Informed Consent: Obtained for all cases.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Aygül Çeltik, Barış Akıncı, Tevfik Demir, Concept: Aygül Çeltik, Barış Akıncı, Tevfik Demir, Design: Aygül Çeltik, Barış Akıncı, Tevfik Demir, Data Collection or Processing: Aygül Çeltik, Barış Akıncı, Tevfik Demir, Analysis or Interpretation: Aygül Çeltik, Barış Akıncı, Tevfik Demir, Literature Search: Aygül Çeltik, Barış Akıncı, Tevfik Demir, Writing Aygül Çeltik, Barış Akıncı, Tevfik Demir.

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