Turkish Journal of Medical Sciences

Volume 42 | Number 2 Article 8

1-1-2012

Mean platelet volume as a marker of future cardiovascular disease risk in pregnant women with impaired fasting glucose and impaired glucose tolerance

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Original Article

Turk J Med Sci
2012; 42 (2): 245-251
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1009-1159

Mean platelet volume as a marker of future cardiovascular disease risk in pregnant women with impaired fasting glucose and impaired glucose tolerance

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Aim: To compare the mean platelet volume (MPV) of pregnant women with mild glycemic disorders with that of healthy pregnant women to find whether these disorders are risk factors for future cardiovascular disease.

Materials and methods: Fasting blood glucose and 50-g oral glucose loading were measured. A 100-g, 3-h oral glucose tolerance test was done when plasma glucose was ≥140 mg/dL, following a loading test. According to the test results, 4 groups were formed: control, impaired fasting glucose, false positive loading test, and impaired glucose tolerance. The hematologic parameters were compared in all of the groups.

Results: The mean MPV of the control group was lower than those of the other groups. The MPV had high sensitivity in prediction of the false positive loading test (sensitivity: 70.0%, specificity: 55.2%, AUC = 0.602, P = 0.029) and impaired glucose tolerance (sensitivity: 73.1%, specificity: 46.1%, AUC = 0.621, P = 0.009), although its sensitivity was lower than the others in prediction of impaired fasting glucose (sensitivity: 60.7%, specificity: 58.2%, AUC = 0.558, P = 0.374).

Conclusion: Mild glycemic disorders are associated with increased MPV. Increased MPV might be associated with elevated baseline cardiovascular risk factors. Individuals with these glycemic disorders might be more aggressively targeted with strategies to lower cardiovascular disease risk.

Key words: Impaired glucose tolerance, impaired fasting glucose, mean platelet volume, cardiovascular disease risk, pregnancy

Bozulmuş açlık glukozu ve bozulmuş glukoz toleransı olan gebe kadınlarda gelecekteki kardiyovasküler hastalık risk belirteci olarak ortalama trombosit hacmi

Amaç: Amacımız hafif glisemik bozukluğu olan gebelerle sağlıklı gebelerin ortalama platelet hacmi (MPV) kıyaslanarak, bu glisemik bozuklukların, gelecekte oluşabilecek kardiovasküler hastalık açısından risk taşıyıp taşımadığını tespit etmekti.

Yöntem ve gereç: Hastaların açlık kan şekeri ölçüldü ve hepsine 50 g oral glukoz yükleme testi yapıldı. Yükleme sonrası sonrası plasma glukozu ≥140 mg/dL ölçülenlere 100-g 3-saatlik oral glukoz tolerans testi uygulandı. Hastalar sonuçlara göre kontrol, bozulmuş açlık glukozu, bozulmuş glukoz toleransı ve yanlış pozitif glukoz yükleme şeklinde 4 gruba ayrıldı. Gruplar hematolojik parametreler açısından kıyaslandı.

Bulgular: Ortalama MPV kontrol grubunda diğer gruplara göre anlamlı derecede düşüktü. MPV'nin sensitivitesi, yanlış pozitif glukoz yükleme (sensitivite: % 70,0; spesifisite: % 55,2; AUC = 0,602; P = 0,029) ve bozulmuş glukoz toleransı (sensitivite: % 73,1; spesifisite: % 46,1; AUC = 0,621; P = 0,009) durumunu tesbit etmede anlamlı şekilde yüksek iken bozulmuş açlık glukozunda diğerlerine göre düşüktü (sensitivite: % 60,7; spesifisite: % 58,2; AUC = 0,558; P = 0,374).

Sonuç: Hafif glisemik bozukluğu olan hastalarda MPV seviyesi artmıştır. MPV değerindeki bu artışın gelecekte oluşabilecek kardiyovasküler hastalık riskinde artışla bir ilgisi olabilir. Bu nedenle bu glisemik bozuklukları olan kadınların, gelecekte oluşabilecek kardiyovasküler hastalık riskini azaltmak için daha ciddi yöntem ve stratejilerle takip edilmeleri uygun olacaktır.

Anahtar sözcükler: Bozulmuş glukoz toleransı, bozulmuş açlık glukozu, ortalama trombosit hacmi, kardiovasküler hastalık riski, gebelik

Received: 16.10.2010 – Accepted: 11.02.2011

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Introduction

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are glycemic disorders and are considered as prediabetic states (1,2). They are used to identify individuals at increased risk for developing diabetes, based on postchallenge or fasting glucose levels, and are associated with varying rates of progression to diabetes and differences in cardiovascular disease (CVD) risk (2).

There are many studies suggesting that in people with type 2 diabetes, cardiovascular mortality is related to the degree of hyperglycemia, and that total mortality is decreased by lowering blood glucose (3,4). A similar association is found among nondiabetic subjects with IFG and IGT. Both IFG and IGT are associated with a modest increase in the risk of CVD, with IGT being a slightly stronger risk predictor (5,6). There is no study in the literature concerning future CVD risk in pregnant women with IFG and IGT. The same risks seen in the nonpregnant population may also be present in pregnant women. In addition, metabolic changes in pregnancy may uncover such a risk earlier.

Mean platelet volume (MPV) is a new and independent risk factor for atherothrombosis and CVD. Many studies have shown that increased MPV is a risk factor for myocardial infarction, cerebral ischaemia, and transient ischaemic attacks (7-9). The measurement of MPV is an important, simple, effortless, and cost-effective tool that should be used for predicting the possibility of impending acute events (10). Patients with larger platelets can easily be identified during routine hematological examination and could possibly benefit from preventive treatment (11).

In considering gestational diabetes mellitus (GDM), the consequences of increased perinatal and maternal morbidity and mortality, in addition to long-term complications and accurate identification of precursors of GDM (IGT and IFG), are of the utmost importance. In this study, we aimed to compare the platelet count and MPV values (an elevated MPV level is an independent risk factor for atherothrombosis and CVD) of pregnant women with IGT or IFG with those of healthy pregnant women, to find out whether these glycemic disorders are risk factors for development of CVD in the future.

Materials and methods

This study was conducted at Fatih University's Department of Obstetrics and Gynecology between January 2008 and October 2009. Patients diagnosed with anemia, hemoglobinopathy, chronic inflammatory disease, renal failure, cyanotic congenital heart diseases, preexisting or gestational diabetes mellitus, other chronic diseases, and preeclampsia were excluded from the study. Informed consent was obtained from all selected subjects.

Fasting blood glucose (FBG) was measured and 50 g of oral glucose loading (OGL) was administered at 24-28 gestational weeks to all participants. FBG <100 mg/dL and plasma glucose <140 mg/dL after OGL were accepted as normoglycemia. When plasma glucose ≥140 mg/dL was measured following the OGL, a 100-g, 3-h oral glucose tolerance test (OGTT) was done. GDM was a plasma glucose level of ≥200 mg/dL 1 h after a 50-g OGL, or ≥2 abnormal plasma glucose values in a 3-h, 100-g OGTT, according to the American Diabetes Association criteria (≥95 mg/dL fasting, ≥180 mg/dL at 1 h, ≥155 mg/dL at 2 h, or ≥140 mg/dL at 3 h) (12). Only 1 value abnormality in the 100-g OGTT was accepted as IGT.

Cases were divided into 4 groups according to their glycemic status. Cases with normal FBG and normal OGL were taken as the control group. Cases with FBG values between 100 and 125 mg/dL and normal OGL were added to the IFG group. Patients with normal FBG but high OGL values and 1 value abnormality in the 100-g OGTT were added to the IGT group. Pregnant women with normal FBG, high OGL, and normal OGTT were added to the false positive OGL group (FP-OGL).

In all cases, systolic and diastolic blood pressures (BPs) were recorded. Hematologic parameters (hemoglobin, hematocrit, red blood cell (RBC) and platelet count, and MPV) were studied. Platelet counts and MPV measurements were performed as part of each full blood count. Samples were taken by antecubital venipuncture into tubes containing tripotassium EDTA. All samples were analyzed on a Beckman/Coulter MAXM hematology analyzer (Beckman Coulter, CA, USA) 2-6 hours after collection to minimize changes in platelet size. The MPV reference range was determined as 7.8-11.0 fL. Strict quality control procedures were adopted;

tri-level controls and external quality assurance programs were used on a regular basis to ensure the accuracy and precision of the instrument.

Data were analyzed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Data were transferred to computer media. Error control and necessary corrections were done. Groups were monitored for conformity to normal distribution by graphical checks and the Shapiro-Wilk test. Mean ± SD was used for parameters that were normally distributed. Median (IQR) was used for groups that were not distributed normally. To examine the differences between groups, one-way analysis of variance was used with the Bonferroni pairwise comparison of means. The Kruskal-Wallis test, followed by the Mann-Whitney U-test with the Bonferroni correction for multiple comparisons, was used for data that did not fulfill the assumptions required for analysis of variance. Receiver operating characteristic (ROC) curve analysis was done to find the sensitivity and specificity of MPV in the prediction of IFG, FP-OGL, IGT, and abnormal OGL results. $P \leq 0.05$ was considered significant.

Results

A total of 222 patients fulfilling the selection criteria were selected and allocated to 4 groups. These included 55 control (24.8%), 56 IFG (25.2%), 60 FP-OGL (27%), and 51 IGT (23%) cases. The mean age, gravity, parity, gestational age, systolic and diastolic BPs, and body mass indexes (BMIs) of the 4 groups were similar (Table 1).

The mean FBG results were 88.7 ± 8.1 mg/dL, 113.5 ± 5.4 mg/dL, 84.1 ± 7.6 mg/dL, and 97.8 ± 11.4 mg/dL in the control, IFG, FP-OGL, and IGT groups, respectively. There was a statistically significant difference between IFG and the other 3 groups. The FBG was significantly higher in that group. Moreover, the FBG of the IGT group was significantly higher than those of the control and FP-OGL groups (Table 1).

The mean OGL results were 106.7 ± 14.8 mg/dL, 124.8 ± 13.4 mg/dL, 158.6 ± 13.8 mg/dL, and 164.7 ± 12.7 mg/dL in the control, IFG, FP-OGL, and IGT groups, respectively (Table 1). There was a significant difference between the control and the other 3 groups

Table 1. Demographic characteristics, FBG, BP, and OGL results of the groups.

	Control	IFG	FP-OGL	IGT	P-value
Age (years)	29.6 ± 4.8	30.1 ± 4.9	29.9 ± 5.4	30.9 ± 6.2	0.612
Gravity (n)	2.0 (IQR = 3)	1.0 (IQR = 1)	2.0 (IQR = 3)	2.0 (IQR = 2)	0.761
Parity (n)	1.0 (IQR = 2)	0.0 (IQR = 1)	1.0 (IQR = 2)	1.0 (IQR = 1)	0.692
G. age (weeks)	25.7 ± 0.3	26.4 ± 0.5	26.1 ± 0.4	25.9 ± 0.5	0.671
BMI (kg/m^2)	25.7 ± 5.1	25.5 ± 4.5	25.9 ± 4.9	26.2 ± 5.3	0.524
OGL (mg/dL)	106.7 ± 14.8	124.8 ± 13.4	158.6 ± 13.8	164.7 ± 12.7	<0.001*
FBG (mg/dL)	88.7 ± 8.1	113.5 ± 5.4	84.1 ± 7.6	97.8 ± 11.4	<0.001¶
SBP (mmHg)	90 (IQR = 20)	95 (IQR = 20)	95 (IQR = 15)	90 (IQR = 18.75)	0.492
DBP (mmHg)	60 (IQR = 10)	60 (IQR = 10)	60 (IQR = 13.75)	60 (IQR = 15)	0.876

*Difference between control versus the other 3 groups and between IFG versus IGT and FP-OGL.
¶Difference between IFG and IGT versus the other 3 groups.

IFG: Impaired fasting glucose
FP-OGL: False positive oral glucose loading
IGT: Impaired glucose tolerance
FBG: Fasting blood glucose
IQR: Interquartile range
SBP: Systolic blood pressure
DBP: Diastolic blood pressure

(P < 0.001). Furthermore, the OGL value of the IFG group was significantly lower than those of the IGT and FP-OGL groups (P < 0.001).

When the groups were compared for hematological parameters, the RBC count, hemoglobin, hematocrit, red cell distribution width (RDW), and platelet distribution width (PDW) values were similar (Table 2). The mean platelet counts in the control, IFG, FP-OGL, and IGT groups were 245.3 ± 68.1, 244.9 ± 58.1, 242.4 ± 60.1, and 235.2 ± 57.2 thousand/mL, respectively. The mean platelet counts were also similar in all of the groups.

The mean MPV values were 8.4 ± 0.9, 8.9 ± 1.1, 8.9 ± 1.3, and 9.1 ± 1.4 fL in the control, IFG, FP-OGL, and IGT groups, respectively. The mean MPV value was significantly lower in the control group than in the other 3 groups. Although the MPV value was higher in the IGT group than in the IFG and FP-OGL groups, no significant differences were found among them (Table 2).

The MPV value had a significantly high sensitivity in the prediction of the false positive loading test (sensitivity: 70.0%, specificity: 55.2%, AUC = 0.602, P = 0.029) and IGT (sensitivity: 73.1%, specificity: 46.1%, AUC = 0.621, P = 0.009), although its sensitivity was lower than the others in prediction of IFG (sensitivity: 60.7%, specificity: 58.2%, AUC = 0.558, P = 0.374). The sensitivity and specificity of MPV in the prediction of IFG, FP-OGL, and IGT are shown in Figures 1 and 3 and Table 3.

Discussion

Our results demonstrated that isolated IGT, IFG, and FP-OGL are associated with increased MPV levels. The MPV value was higher in the IGT group than in the FP-OGL and IFG groups, although this difference between groups was not significant. According to our results, as glucose intolerance worsens, the MPV level increases. In other words, the higher the degree of glucose intolerance, the higher the level of MPV. These results are important because they indicate the influence of glucose intolerance on MPV, regardless of the degree of the intolerance. This increase in MPV might be associated with an elevated baseline CVD risk.

A high MPV is an important risk factor for atherothrombosis, thromboembolism, and CVD (7-10). A high MPV level alone may not demonstrate a CVD risk, but it might caution us about CVD risk and the investigation of other risk factors of CVD. In this way, present or future CVD risk and possible complications could be determined and prevented earlier.

Table 2. Hematological findings of the groups.

	Control	IFG	FP-OGL	IGT	P-value
Hemoglobin (g/dL)	12.1 ± 1.2	11.9 ± 1.2	12.4 ± 1.4	12.4 ± 0.9	0.614
Hematocrit (%)	35.3 ± 3.4	34.4 ± 3.6	36.2 ± 3.8	35.1 ± 2.8	0.342
Platelets ($\times 10^9$/L)	245.3 ± 68.1	244.9 ± 58.1	242.4 ± 60.1	235.2 ± 57.2	0.620
Red blood count ($\times 10^{12}$/L)	4.2 ± 0.5	4.5 ± 0.5	4.1 ± 0.6	4.2 ± 0.4	0.338
Platelet distribution width (PDW) (%)	16.1 ± 1.5	16.6 ± 1.0	16.4 ± 1.7	16.2 ± 1.5	0.435
Red cell distribution width (RDW) (%)	13.8 ± 2.1	13.5 ± 2.5	13.1 ± 2.0	13.3 ± 1.4	0.335
Mean platelet volume (MPV) (fL)	8.4 ± 0.9	8.9 ± 1.1	8.9 ± 1.3	9.1 ± 1.4	0.029* 0.002¶ 0.028‡

*Between the control and IFG
¶Between the control and IGT
‡Between the control and FP-OGL
IFG: Impaired fasting glucose
FP-OGL: False positive oral glucose loading
IGT: Impaired glucose tolerance

Table 3. Sensitivity, specificity, AUC, and cut-off value of MPV in prediction of IFG and FP-OGL.

Group	Cut-off MPV (fL)	Sensitivity (%)	Specificity (%)	AUC	P-value	CI
IFG	8.75	60.7	58.2	0.558	0.374	0.437-0.679
FP-OGL	8.45	70.0	55.2	0.602	0.029	0.509-0.695
IGT	8.45	73.1	46.1	0.621	0.009	0.530-0.712

P < 0.05 statistically significant
AUC: Area under the curve
CI: Confidence interval
MPV: Mean platelet value
IFG: Impaired fasting glucose
FP-OGL: False positive oral glucose loading
IGT: Impaired glucose tolerance

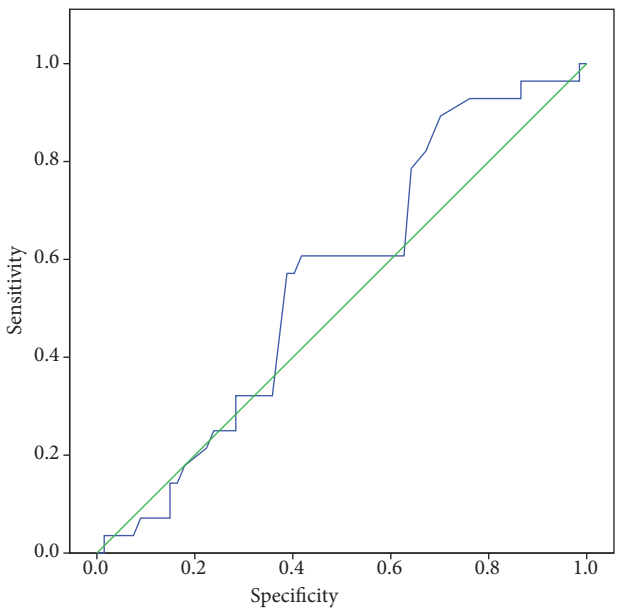

Figure 1. Sensitivity and specificity of MPV for IFG.

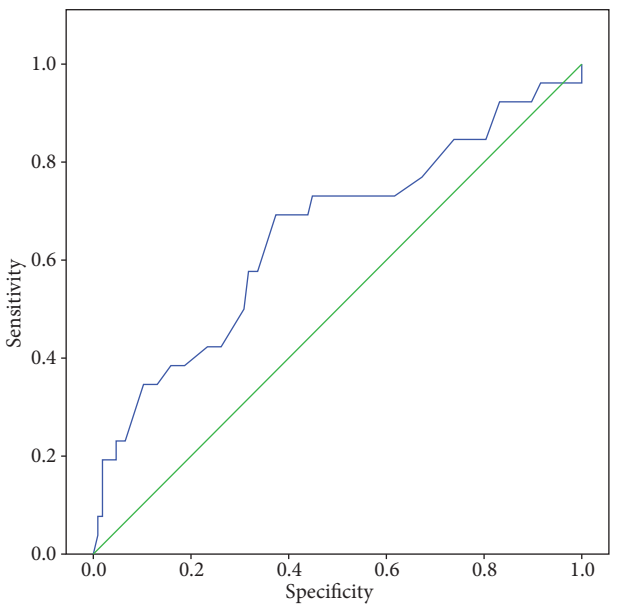

Figure 2. Sensitivity and specificity of MPV for FP-OGL.

In a collaborative data analysis of 6766 subjects from 5 Finnish cohorts, it was shown that the survival profile for coronary heart disease incidence and CVD mortality was similar for IGT and for newly diagnosed diabetes, which were worse than that for IFG (13).

The MPV values were higher in diabetic cases, and with the decrease in blood glucose, a significant fall was observed in the MPV values (14). In a study done by Zuberi et al. (15), the MPV values of the diabetes mellitus (DM), non-DM, and IFG groups were compared. They observed significant differences in the MPV levels among all of the groups.

In a similar study done by Coban et al. (16), the MPV was significantly higher in diabetic and IFG groups versus the control group. Platelet counts were not different among the study groups. The MPV and platelet mass were positively correlated with fasting glucose and HbA1c in the diabetic and IFG groups. It has been suggested that subjects with IGT tend to have increased platelet activation (17). Increased platelet activity could contribute to increased risk of cardiovascular disease in IGT and IFG.

Just like in the nonpregnant population, IFG and IGT in pregnancy may indicate future CVD risk. No studies were found in the literature concerning the

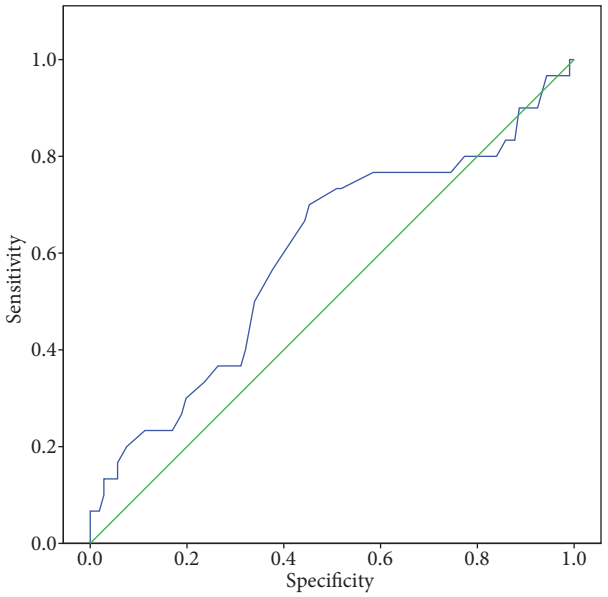

Figure 3. Sensitivity and specificity of MPV for IGT.

future risk of CVD in pregnant women with IGT and IFG. Glucose intolerance during pregnancy may be an early sign of metabolic disease later in the life. Becoming pregnant is a good challenge for women to assess their metabolic state. Because pregnancy itself induces excessive metabolic changes, women who tolerate this changes successfully (healthy pregnant women) can be accepted as having lower CVD risk in the future if no other risk factors are present. Women who tolerate these changes poorly (women with GDM, IGT, and IFG) would be expected to be at risk of future CVD. Physicians must be vigilant for the development of glucose intolerance, especially in patients with high MPV, and screening for glycemic disorders might be done in these patients before 24 weeks, if necessary. Therefore, an existing glucose intolerance could be detected and treated earlier and possible fetal and maternal complications could be prevented.

A number of limitations in this study deserve comment. First, the study groups were quite modest in size, so it is possible that the study was underpowered to detect differences among all of the groups. Second, we only used MPV as a marker of future CVD. However, other risk factors that can modify CVD must also be assessed separately. Third, long-term follow-up of the cases is very important to correctly stratify the future risk.

Conclusion

Individuals with IFG and IGT that are accepted as prediabetic and cases of FP-OGL, which is a lesser degree of glucose intolerance, should be targeted more aggressively with strategies to lower CVD risk. A high MPV may be a warning for this. Long-term studies are necessary to confirm that women with these glycemic disorders have increased cardiac morbidity and mortality and to define a potential role for lifestyle and/or pharmacological intervention.

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