Mean platelet volume in diagnosis of gestational diabetes

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ABSTRACT

Gestational diabetes mellitus (GDM) prevalence is within range of 1-14%, varying relative to the countries and ethnic groups. By many studies, mean platelet volume (MPV) has been shown to be higher in GDM and Type II diabetes mellitus patients. Our aim is to evaluate the sensitivity and specificity of MPV in GDM screening. The study population was consisted of pregnant women aged above 18 years with a singleton pregnancy at 24 to 28 weeks of gestation. Three hundred patients complying with the study criteria were split into 3 groups as follows: Group 1, 219 pregnant patients with normal 50g oral glucose tolerance test (OGTT) result; Group 2, 23 pregnant patients diagnosed with impaired glucose tolerance based on the OGTT result; and Group 3, 58 pregnant patients diagnosed with GDM. MPV measurement was started with collecting 2 ml blood samples into K3 Etilendiamintetraasetikasit (EDTA) tubes from each patient. The statistical analyses were done with statistical package for the social sciences (SPSS) 20.0 package program. In our study, the optimal cut-off MPV value for GDM prediction was >8.8 fL. The specificity and negative predictive value of MPV at >8,8 fL were 75.9% and 38.9%, respectively. GDM patients may exhibit significant changes in MPV and hemoglobin A1c (HbA1c) values. Future randomized studies will be helpful in developing a MPV-related diagnostic test, adjusting the treatment, predicting the complications, and taking preventive measures in GDM patients.

1. Introduction

Gestational diabetes mellitus (GDM) and Impaired Glucose Tolerance (IGT) are the most common metabolic disorders seen during pregnancy which have importance because they may lead to fetal and maternal complications. GDM prevalence occurs within range of 1-14%, varying relative to the countries and ethnic groups. The developing risk of Type II DM within 5-16 years in women with GDM is 17-63% (Mazze and Krogh, 1992, Harris et al., 1997).

By many studies, mean platelet volume (MPV) has been shown to be higher in GDM and Type II diabetes mellitus patients than in the normal population (Hekimsoy et al., 2004; Papanas et al. 2004). Two different theories are discussed for the underlying mechanism of elevated platelet volume. One of these theories is based on osmotic swelling due to increased blood glucose concentration and elevated levels of some glucose metabolites. Another possible mechanism focuses on increased platelet turnover associated with platelet hyperactivity. In diabetic patients, the amount of intracellular free calcium and calcium release from platelets increase, thereby leading to the activation of arachidonic pathway which increases the formation of thromboxane A2 (TxA2). TxA2 activity, in turn, causes thrombopoietic stress associated with platelet hyperactivity and raised turnover, giving rise to megakaryocytic growth.

Granules of larger platelets secrete higher amount of serotonin and β tromboglobulin, and produce higher volume of TxA_2 (Bath and Butterworth, 1996). Furthermore, they contain higher amounts of similar adhesion molecules such as P-selectin and glycoprotein IIb/IIIa (Jagroop and Mikhailidis, 2001). Large platelets have higher activity and are more prone to adhesion and aggregation (Hekimsoy et al., 2004; Park et al., 2002). Therefore, MPV alone is recognized as a marker of the platelet activation process (Bath and Butterworth, 1996).

Our primary end point in this study is to investigate the relationship of MPV levels with blood sugar and hemoglobin concentrations, whereas our second end point is to evaluate the sensitivity and specificity of MPV in GDM screening.

2. Materials and methods

This study was conducted at the Izmir Ege Gynecology and Obstetrics Teaching and Research Hospital between January 2012 and June 2012. The study population was consisted of pregnant women aged above 18 years with a singleton pregnancy at 24 to 28 weeks of gestation. Exclusion criteria were as follows: Pregestational diabetes; multiple pregnancy; hemoglobinopathy; hematologic, hypertensive, or chronic inflammatory disease; an endocrine disease that may cause diabetes, and smoking cigarette. Informed consent was obtained from all women prior to inclusion in the study, which was approved by the Local Human Investigation Committee.

Subsequent to a fasting period of 8-14 hours, blood was collected from the pregnant women and 1-hour oral glucose tolerance test (OGTT) was performed with standard 50 g glucose (Glucose, Dextrose Monohydrat 50 g). Glucose measurement was carried out from venous blood using the enzymatic method. The cut-off value for 1-hour glucose tolerance test after 50g glucose load was defined as 140 mg/dL. The glucose levels above 180 mg/dL were recognized as GDM. The women with a glucose value between 140-180 mg/dL underwent 100g 3-hour OGTT test. GDM diagnosis was based on Carpenter and Coustan criteria (C&C), as exceeding two of the threshold values for OGTT. In cases where only one threshold was exceeded, the diagnosis was impaired glucose tolerance (Table 1).

Table 1. Threshold values used in 100g OGTT test in GDM diagnosis based on the Carpenter and Coustan (C&C) criteria

Fasting plasma glucose	≥95 mg/dL
Plasma glucose at 1 hour	≥180 mg/dL
Plasma glucose at 2 hours	≥155 mg/dL
Plasma glucose at 3 hours	≥140 mg/dL

GDM: Gestational diabetes mellitus; **OGTT:** Oral glucose tolerance test

MPV measurement was started with collecting 2 ml blood samples into K3 EDTA tubes from each patient. The analysis was performed by Beckman Coulter device within 2 hours from the collection, while HbA1c was studied with immunoturbidimetric inhibition method.

The statistical analyses were done with SPSS 20.0 package program. The distribution of the data was tested with Kolmogorov-Smirnov. The variables were analyzed with ANOVA (Tukey test), whereas covariates were studied with MANCOVA, and correlation analysis was carried out with Pearson's correlation analysis. $p < 0.05$ is considered to be statistically significant.

3. Results

A total of 300 patients complying with the study criteria were split into 3 groups as follows: The Group 1, 219 pregnant patients with normal 50g OGTT result; the Group 2, 23 pregnant patients diagnosed with impaired glucose tolerance based on the OGTT result; and the Group 3, 58 pregnant patients diagnosed with GDM.

The Group 1 had significantly lower mean age than Groups 2 and 3 ($p < 0.05$), whereas the Group 2 showed significantly higher gestational age as compared to the Groups 1 and 3 ($p < 0.05$) (Table 2).

The hemoglobin value showed a homogenous distribution among the groups, while MPV value was significantly higher in the Group 3 than in the Groups 1 and 2, and HbA1c value was significantly higher in the Groups 2 and 3 than in Group 1 ($p < 0.05$) (Table 3).

Table 2. Comparison of the groups with regard to age and gestational age

	Group 1	Group 2	Group 3	p
	Mean ± s.d	Mean ± s.d	Mean ± s.d	
Age	25.75±5.20	29.22±4.72	30.12±4.68	0.000
Gestational age	25.42±1.40	26.57±2.21	25.50±1.31	0.017
ANOVA (Tukey test)				

The comparison of the three groups with regard to MPV, HbA1c, and fasting blood glucose (FBG) levels, independent of age and gestational week, revealed that MPV was significantly higher in the Group 3 than in the Groups 1 and 2, whereas HbA1c was significantly higher in Group 1 than in Groups 2 and 3 ($p < 0.05$) (Table 4).

Table 3. Comparison of the groups with regard to Hb, MPV, HbA1c and fasting plasma glucose

	Group 1	Group 2	Group 3	p
	Mean ± s.d	Mean ± s.d	Mean ± s.d	
Hb	11.55±0.93	11.43±0.90	11.62±0.77	0.831
MPV	8.53±0.99	8.35±1.34	9.43±1.09	0.000
HbA1c	4.94±0.26	5.17±0.65	5.02±0.52	0.000
Fasting plasma glucose	81.74±9.27	86.09±7.87	92.47±11.45	0.000

ANOVA (Tukey test); MPV: Mean platelet volume; **HbA1c:** Hemoglobin A1c

Gestational diabetes risk was observed to rise 1.155-fold (1.090-1.224) for each one year increase in age, 2.098-fold (1.586-2.776) for each unit of increase in MPV, 3.509-fold (1.371-8.892) for each unit of increase in HbA1c, and 1,098-fold (1.064-1.134) for each unit of increase in FBG (Table 5).

In the ROC analysis, the area under the curve exhibited significant results at all MPV cut-off values within 8-10 fL range. The highest area under the curve was determined at 8.5-8 fL range. The MPV cut-off value of >8.8 fL showed the highest area under the curve.

Table 4. Comparison of the groups with regard to MPV, HbA1c, and fasting plasma glucose levels, independent of age and gestational week

	Group 1			Group 2			Group 3			p
	Mean	Lowest	Highest	Mean	Lowest	Highest	Mean	Lowest	Mean	
MPV	8.5	8.4	8.7	8.4	8.0	8.8	9.4	9.2	9.7	0.000
HbA1c	4.8	4.7	4.8	5.0	4.9	5.2	5.0	4.9	5.1	0000
Fasting plasma glucose	82.1	80.8	83.4	85.5	81.5	89.5	91.4	88.9	94.0	0.000

Mancova (LCD), MPV: Mean platelet volume; **HbA1c:** Hemoglobin A1c

Table 5. The effects of age, MPV, HbA$_{1c}$ and fasting plasma glucose levels on GDM development

	OR	%95 Confidence interval Lowest	Highest	p
Age	1.155	1.090	1.224	0.000
MPV	2.098	1.586	2.776	0.000
HbA1c	3.509	1.371	8.982	0.009
Fasting plasma glucose	1.098	1.064	1.134	0.000

MPV: Mean platelet volume; **HbA1c:** Hemoglobin A1c; **GDM:** Gestational diabetes mellitus

The specificity and negative predictive value of mean platelet volume (MPV) values above 8.8 fL for GDM detection were 75.9% and 38.9%, respectively (Table 6).

Table 6. The sensitivity and specificity of MPV cut-off values

			Gestational DM -	+
MPV	≤8.8	N	173	14
		% (in total)	92.5%	7.5%
		% (in GDM)		24.1%
	>8.8	N	69	44
		% (in total)	61.1%	38.9%
		% (in GDM)		75.9%

MPV: Mean platelet volume; **GDM:** Gestational diabetes mellitus

4. Discussion

In this study comparing pregnant women with and without GDM, the MPV values were found to be significantly higher in the GDM group than in the IGT and control groups. There was no significant difference between the IGT and control groups with regard to MPV value. Each unit of increase in MPV was observed to raise the risk of GDM by 2.098-fold (1.586-2.776).

Platelet volume is an indicator of platelet function and activation, and it is evaluated by MPV measurement (Sharp and Trinick, 1993; Demirtunç et al., 2009). Previous studies have shown higher MPV levels in non-pregnant Type II diabetic patients, as compared to the general population(Jirapinyo et al., 1993; Piazze et al., 2006). The risk factors and development of GDM appear to be similar to those of Type II DM. As in Type II DM patients, GDM patients may exhibit significant changes in MPV and hemoglobin A1c (HbA1c) values (Akyol et al., 2008). Compared to the platelets with normal volume, large platelets appear to show higher level of metabolic activity. Therefore, studies have shown raised TxA2 and low prostacyclin (PG12) levels, leading to vasoconstriction in both maternal and fetal circulation (Çoban et al., 2006; Crowther et al., 2005) Elevated MPV is recognized

as an important marker of raised blood sugar level in GDM patients and it is held responsible for the microvascular and macrovascular complications.

In this study, HbA1c and fasting plasma glucose levels were significantly higher in the patients diagnosed with GDM and IGT than in the controls, and MPV demonstrated no significant correlation with HbA1c and FBG. HbA1c and FBG levels were lower than those noted in the Type II DM diagnostic criteria in the patients with GDM and IGT, however, the differences were statistically significant as compared to the control group. The patients with Type II DM had higher levels of FBG as compared to the patients with GDM and IGT, which may be the reason why MPV did not exhibit a significant correlation with HbA1c and FBG. The rarity of vascular complications in the GDM patients as compared to the Type II DM patients may be associated with this.

In our study, the optimal cut-off MPV value for GDM prediction was >8.8 fL. The specificity and negative predictive value of MPV at >8,8 fL were 75.9% and 38.9%, respectively. Jirapinyo et al. conducted a study on 396 women with high-risk pregnancy and the sensitivity and specificity of the 50g OGT test for GDM detection were found to be 85.7% and 65%, respectively (Jirapinyo et al., 1993). More detailed studies including larger samples may be performed to compare the efficacy of MPV and 50g OGT in GDM detection, and to further evaluate the utility of MPV as a GDM screening test.

Since MPV is a marker of platelet activation, elevated MPV levels may help us in predicting secondary vascular complications.

Pregnant women with GDM are at high risk for development of hypertension and pre-eclampsia (Yogev and Visser, 2009). Dundar et al. performed a study on 1336 pregnant women and found that the sensitivity and specificity of MPV at >8.5 fL was 78% and 86%, respectively (Dundar et al., 2008) In the study of Piazze et al. including 61 women with pregnancy-related hypertension and 122 controls, MPV was observed to be significantly higher in the hypertension group (Piazze et al., 2006). Future studies of similar design including GDM patients may be beneficial in predicting pre-eclampsia.

Gestational diabetes mellitus is a metabolic disorder characterized with varying degrees of carbohydrate intolerance. The patients with GDM diagnosis should be followed closely during the antenatal period with regard to maternal and fetal complications that may arise due to hyperglycemia. The assessment of platelet functions is increasingly used in predicting these complications. We believe that future randomized studies will be helpful in developing a MPV-related diagnostic test, adjusting the treatment, predicting the complications, and taking preventive measures in GDM patients.

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