Relationship between mean platelet volume and vitamin D deficiency in gestational *diabetes mellitus*

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ABSTRACT

Objective: To investigate whether vitamin D deficiency is associated with high mean platelet volume (MPV) in pregnancies diagnosed with gestational *diabetes mellitus* (GDM) compared to healthy pregnancies. **Subjects and methods:** This study included 200 pregnant women. 25-hydroxyvitamin D_3 (25(OH)D_3) and MPV values were monitored between pregnant women with GDM and normal glucose metabolism. Correlation between 25(OH)D_3 and MPV was calculated both in GDM and healthy pregnancies. Both 25(OH)D_3 level in different MPV percentile (≤ 50, 50-75, 75-90, ≥ 90 percentile) and MPV value in different 25(OH)D_3 level (≤ 10, 10-20, ≥ 20 ng/mL) were calculated. **Results:** Low 25(OH)D_3 level and high MPV were observed both in GDM group (p = 0.007, p = 0.06, respectively) and in glucose metabolism disorders (GMD) group (p = 0.03, p = 0.04, respectively). There was no significant relationship between 25(OH)D_3 and MPV in healthy pregnancies. Whereas, it is observed that there is a negative, but statistically insignificant correlation between MPV and 25(OH)D_3 pregnant women with GMD (r = 0.1, r = -0.7, respectively). MPV values had significantly higher in vitamin D deficient group than pregnant women with normal 25(OH)D_3 level in GMD group (p = 0.04). The optimal 25(OH)D_3 cut off point for predicting future cardiovascular risk was 10.4 ng/ mL (area under curve (AUC) = 0.58). **Conclusions:** Vitamin D deficiency may contribute to an increased risk for future cardiovascular diseases and a risk of thrombotic complications in pregnant women with GDM. Arch Endocrinol Metab. 2015;59(5):448-54

Keywords
Gestational *diabetes mellitus*; vitamin D deficiency; mean platelet volume

INTRODUCTION

GDM is defined as glucose intolerance that is first recognized during pregnancy and confers a 4- to 7-fold greater risk of incident type 2 *diabetes mellitus* with an increased risk of developing the metabolic syndrome in midlife (1-3). A previous history of GDM not only increases a woman's risk of future metabolic disease, but has been linked to elevated heart disease risk in women as well (4,5). Studies have reported a 66% to 85% higher risk of cardiovascular diseases, including coronary artery disease, myocardial infarction, and/or stroke in women who have a history of GDM (6).

Longitudinal studies have demonstrated increased cardiovascular mortality and morbidity associated with vitamin D deficiency. Low vitamin D levels have been linked to inflammation, higher coronary artery calcium scores, impaired endothelial function, and increased vascular stiffness (7-9). Furthermore, there is an increasing interest in the relationship between vitamin D and GDM. Several studies have reported lower vitamin D levels in women with GDM, but the underlying mechanism between vitamin D and GDM is unclear (10-13).

Altered platelet morphology and function have been reported in patients with metabolic syndrome, stroke, and *diabetes mellitus*. Recent studies have demonstrated that an increase in MPV has been documented in patients with GDM and increased MPV is now emerging as an independent risk factor for future thromboembolism and myocardial infarction (14,15). Furthermore, new evidence has suggested that vitamin D may play an important role in preventing platelet activation as well as decreasing fibrinolysis and thrombosis. Thus vitamin D deficiency may lead to an increased MPV (16). In a new study it has been demonstrated that there is a strong association between a low vitamin D level and a high MPV in healthy volunteers (17).

Although most women maintain a normal platelet count throughout gestation in normal pregnancy, the normal range of platelet counts decreases. Increased

blood volume, an increase in platelet activation, and increased platelet clearance all contribute to a "physiologic" decrease in the platelet count. Furthermore, MPV and platelet count show an inverse relationship. Average platelet size is larger when an increase in platelet production occurs. Thus, platelet lifespan declines and the MPV increases minimally during pregnancy (18,19).

In this study we aimed at assessing the relationship between the MPV value and vitamin D level of pregnant women with GDM in order to determine whether vitamin D deficiency in GDM may be a risk factor for future development of cardiovascular diseases.

SUBJECTS AND METHODS

This present study was approved by the local ethical committee at the Sifa University. Written participation consents were obtained, and the procedures followed were in accordance with the Helsinki Declaration of 1975 (revised in 2008). Data were collected between May 2012 and November 2012.

During the study period, there were 142 vaginal and 204 caesarean section deliveries in our clinic. Female volunteers at 24-28 weeks of pregnancy were evaluated for the study (source population, n = 297). Subjects with *diabetes mellitus*, hypertension, anemia, haemoglobinopathy, chronic liver disease, chronic renal disease, rheumatic disease, gastrointestinal diseases with malabsorption, subjects who smoked, as well as subjects on chronic medical therapy and with other chronic diseases were excluded from the study. Pregnant women who were on calcium and vitamin D supplements were also excluded from the study. Two hundred patients who met the criteria were enrolled in the study.

Body mass index (BMI (weight (kg)/height $(m)^2$) was calculated by measuring the height and the body weight at the sample time.

The participants were questioned about their frequency of exposure to sunlight (between 10:00 to 15:00 h) in terms of number of days of exposure in a week, not less than 30 minutes.

The participants were questioned about their clothing style. Covered clothing style was defined as clothing covering all body parts except for the hands and face.

In our study, all pregnant women in the 24^{th}-28^{th} week of pregnancy were screened for GDM. The criteria used for the diagnosis of GDM were defined in the National Diabetes Data Group (NDDG) (18). A one hour-50 gr oral glucose challenge test (GCT) was applied to all pregnant subjects regardless of their fasting conditions. After a fasting of 8 hours and between 8:00-9:00 AM, a 3-hour 100 gram oral glucose tolerance test (OGTT) was applied to pregnant subjects whose GCT is ≥ 140 mg/dL. Fasting blood glucose (FBG) and glucose levels at the 1^{st}, 2^{nd}, and 3^{rd} hour were controlled. Patients exhibiting one of the following high values were diagnosed with impaired glucose tolerance (IGT): FBG ≥ 105 mg/dL, 1^{st} hour ≥ 190 mg/dL, 2^{nd} hour ≥ 165 mg/dL, 3^{rd} hour ≥ 145 mg/dL. Those with a minimum of 2 high values were diagnosed with the GDM. IGT and GDM groups were addressed as glucose metabolism disorders (GMD) in the gestation period (20).

In all cases, platelet count and MPV were performed as part of each full blood count. Samples were taken by antecubital venipuncture into tubes containing tripotassium ethylenediaminetetraacetic acid (EDTA). All samples were analyzed by using an automated analyzer (Sysmex SE 9500; Roche, Indianapolis, IN). The samples were rapidly processed (within less than 1 h) in order to minimize platelet swelling in the test tubes. 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.

The best indicator of vitamin D status is the serum $25(OH)D_3$ concentration, because it reflects both dietary intake from vitamin D and cutaneous synthesis of vitamin D. Therefore we examined the serum $25(OH)D_3$ concentration. Serum $25(OH)D_3$ level was analyzed with ELISA (EUROIMMUN, D-23560 Lübeck, Seekamp 31, Germany) method. There is no absolute consensus as to what a normal range for $25(OH)D_3$ should be in pregnancy. In recent years, most authors agree that vitamin D deficiency in pregnancy should be defined by a $25(OH)D_3$ level of ≤ 20 ng/mL and vitamin D insufficiency should be defined by a $25(OH)D_3$ ≥ 20 to < 32 ng/mL (21). But, when we look at our regional data, we have seen that vitamin D levels of pregnant women were significantly lower than the international values (22,23). Furthermore, only six of 200 pregnant women (3%) had vitamin D level more than 32 ng/mL in our study. Therefore, we accepted the value range for vitamin D deficiency is ≤ 10 ng/mL and for vitamin D insufficiency is > 10 to ≤ 20 ng/mL like national studies (Figure 1).

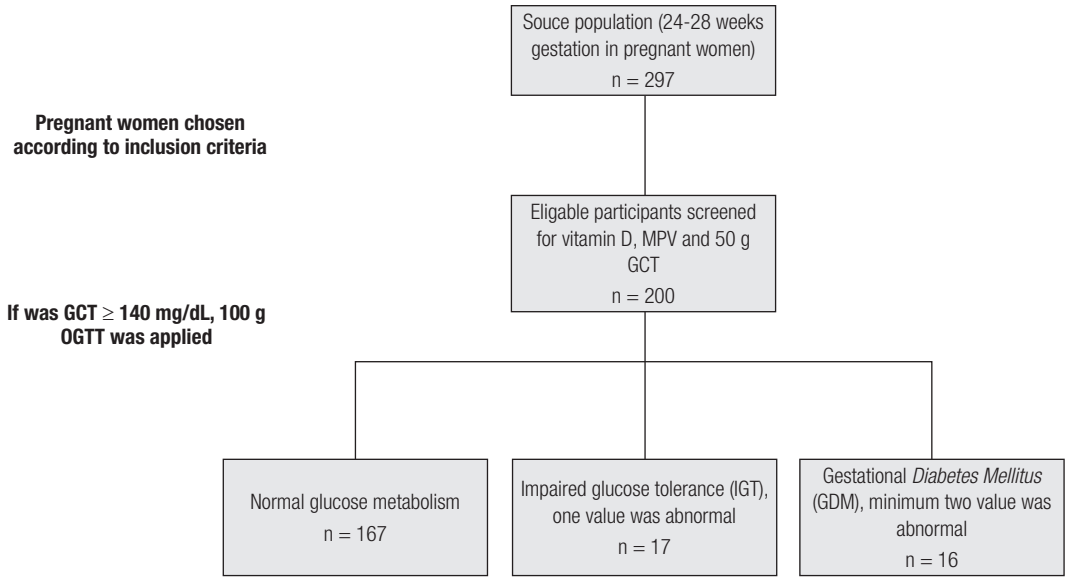

Figure 1. Represents a flow chart of the study design. (IGT + GDM = Glucose metabolism disorder – GMD – group, n = 33).

Statistical analysis

Statistical analysis was performed by using SPSS (15.0) for Windows. The mean ± SD was used for parameters that were normally distributed. The median was used for groups that were not distributed normally. To examine the differences between groups, one-way analysis of variance was used with the Duncan 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 the analysis of variance. Pearson's correlation coefficient was used for evaluating the relationships between MPV and $25(OH)D_3$ in normal glucose metabolism and glucose metabolism disorders groups. Because the goodness-of-fit tests for normal distribution of the MPV showed that the MPV was not normally distributed (P, 0.01), the median (interquartile) for MPV was used in the descriptive analyses. ANOVA test was used to investigate whether the MPV value has changed in different levels of $25(OH)D_3$. Receiver operating characteristic (ROC) curve analysis was used for determining the discriminating $25(OH)D_3$ cut off value in order to predict the future cardiovascular risk in the GDM group. The MPV value indicating future cardiovascular risk was considered to be 8.7 fl (24). A *p* value of 0.05 was considered to be statistically significant.

RESULTS

A total of 200 pregnant women who met the inclusion criteria were enrolled in the study out of a total population of 297.

Basic characteristics of gestational groups with and without gestational glucose metabolism disorder are presented in table 1. The $25(OH)D_3$ level and platelet count were significantly low in the GDM group (p = 0.007, p = 0.01). Twenty three (13.7%) pregnant women with normal glucose metabolism and 15 (45.4%) pregnant women with GMD had vitamin D deficiency. MPV was higher in the GDM group than the IGT and normal glucose metabolism group, but it was not statistically significant (p = 0.06). However, when considered together with the IGT and GDM group as well as the GMD group, a low $25(OH)D_3$ level and high MPV value were found in the GMD group (p = 0.03, p = 0.04, respectively).

When considering the percentile groups separated (MPV ≤ 50, 50-75, 75-90, ≥ 90), there was no difference observed for $25(OH)D_3$ levels in pregnant women with normal glucose metabolism (p = 0.3). When the same analysis was performed in pregnant women with GMD, there was an inverse relationship observed between $25(OH)D_3$ levels and MPV percentile, however these data did not reach statistical significance (p = 0.07; Table 2).

In addition, there was a weak and statistically insignificant correlation between MPV and 25(OH)D_3 in pregnant women with normal glucose metabolism (r = 0.1, p = 0.6). Nevertheless, there was a negative correlation with MPV and 25(OH)D_3 in pregnant women with complicated GMD, but these values did not reach statistical significance (r = -0.7, p = 0.06; Table 3).

When examining 25(OH)D_3 levels by dividing them among deficiency, insufficiency, and normal, the MPV values observed did not differ significantly in women with normal glucose metabolism (p = 0.9). On the other hand, MPV values were significantly higher in the vitamin D deficient group than pregnant women with normal 25(OH)D_3 levels in the GMD group (p = 0.04; Table 4).

The prognostic value of the 25(OH)D_3 level was determined by using ROC curves in the GDM group (Figure 2). MPV value indicating future cardiovascular risk was considered to be 8.7 fl (24). Based on ROC curve analysis, the optimal cut off points for predicting future cardiovascular risk was 10.4 ng/mL (AUC = 0.58).

Table 1. Characteristics, vitamin D level and hematologic parameters of normal glucose metabolism and glucose metabolism disorders groups (mean ± SD)

	Normal glucose metabolism n = 167	IGT n = 17	GDM n = 16	P1	GMD n = 33	P2
Age (yr)	28.7 (5)	28.2 (3.6)	29 (3.1)	0.08	28.4 (3.0)	0.6
Gestational week	24.9 (0.9)	24.8 (1)	24.9 (0.9)	0.2	24.8 (1)	0.9
BMI	26.6 (3.5)	26.8 (3.1)	27.1 (3.6)	0.8	26.9 (3.5)	0.4
Sun exposure, ≥ 3 day/week and ≥ 30 min/day n,%	54, 32.3	6, 35.3	5, 31.2	0.7	12, 36.3	0.8
Covered clothing style n,%	82, 49.1	9, 52.9	9, 56,2	0.09	18, 54.5	0.06
Mean vitamin D level (ng/mL)	21.6 (10.7)[a]	20.9 (14.3)[a]	15.5(16.1)[b]	**0.007**	17.1 (15.3)	**0.03**
Vitamin D deficiency (≤ 10 ng/mL) (n, %)	23, 13.7[a]	8, 47[b]	7, 43.7[b]	**< 0.01**	15, 45.4	**< 0.01**
Vitamin D insufficiency (10-20 ng/mL) (n,%)	88, 52.6[a]	5, 29.4[b]	6, 37.5[b]	**< 0.01**	11, 33.3	**< 0.01**
Normal level (≥ 20 ng/mL) (n, %)	56,33.5[a]	3, 17.6[b]	4, 25[c]	**0.05**	7, 21.2	**0.04**
MPV (fL)	9.6 (1)	9.8 (0.7)	10.9 (1)	0.06	10.5 (0.9)	**0.04**
Hb (g/dL)	12 (1)	11.8 (1)	12.1 (0.8)	0.3	12 (0.9)	0.4
Platelets (×109/L)	235 (52)[a]	248 (74)[b]	228 (34)[c]	**0.01**	234 (42)	0.7

IGT: impaired glucose tolerance, GDM: gestational *diabetes mellitus*, GMD: glucose metabolism disorders, MPV: mean platelet volume, BMI: body mass index, Hb: hemoglobin. p < 0.05 is statistically significant. P1: the relationship between normal glucose metabolism, IGT and GDM groups, P2: The relationship between normal glucose metabolism and GMD group. The results demonstrating statistically significant difference was shown with different superscripts.

Table 2. Vitamin D level by MPV quartile

MPV quartile (MPV, n)	Mean vitamin D level in normal glucose metabolism n = 167 (±SD, %95 confidence interval)	P_1	MPV quartile (MPV, n)	Mean vitamin D level in GMD n = 33 (±SD, %95 confidence interval)	P_2
≤ 50 percentile (9.8, 103)	19.9 (10.3, 18-21.9)	0.3	≤ 50 percentile (9.6, 7)	20.7 (10.1, 16-21.7)	0.07
50-75 percentile (10.5, 36)	22.5 (10.6, 19.4-25.7)		50-75 percentile (10.8, 12)	19.9 (11.2, 17.2-23)	
75-90 percentile (11.3, 24)	23 (12.9, 18.4-27.5)		75-90 percentile (12, 10)	17.4 (9.9, 16-19.9)	
≥ 90 percentile (12.2, 4)	23.2 (9, 17.7-28.7)		≥ 90 percentile (12.5, 4)	16.1 (10.3, 15.8-19)	

P values were obtained by ANOVA. P1: In pregnant women with normal glucose metabolism, P2: In pregnant women with glucose metabolism disorders (IGT+GDM = GMD) group. MPV: mean platelet volume. P < 0.05 is statistically significant.

Table 3. Correlations of MPV and vitamin D in normal glucose metabolism and glucose metabolism disorders groups

	Normal glucose metabolism n = 167	Glucose metabolism disorders (IGT+GDM) n = 33
MPV – Vitamin D correlation coefficient (r)	r = 0.1	r = -0.7
p	0.6	0.06

IGT: impaired glucose tolerance, GDM: Gestational *diabetes mellitus*, MPV: mean platelet volume. Pearson correlation test was used. P < 0.05 is statistically significant.

Table 4. MPV level in pregnant women with different vitamin D level

		Vitamin D deficiency (≤ 10 ng/mL)	Vitamin D insufficiency (10-20 ng/mL)	Normal level (≥ 20 ng/mL)	P
Normal glucose metabolism n = 167	MPV (mean ± SD)	10.0 (1) n = 23	9.8 (0.8) n = 88	9.9 (0.9) n = 56	0.9
Glucose metabolism disorders (IGT+GDM) n = 33	MPV (mean ± SD)	12.1 (1.1)[a] n = 15	10.5 (1)[b] n = 11	9.7 (0.8)[b] n = 7	0.04

First line = pregnant women with normal glucose metabolism, second line = pregnant women with glucose metabolism disorders (IGT+GDM). MPV: mean platelet volume. ANOVA test was used. P < 0.05 is statistically significant. The results demonstrating statistically significant difference was shown with different superscripts.

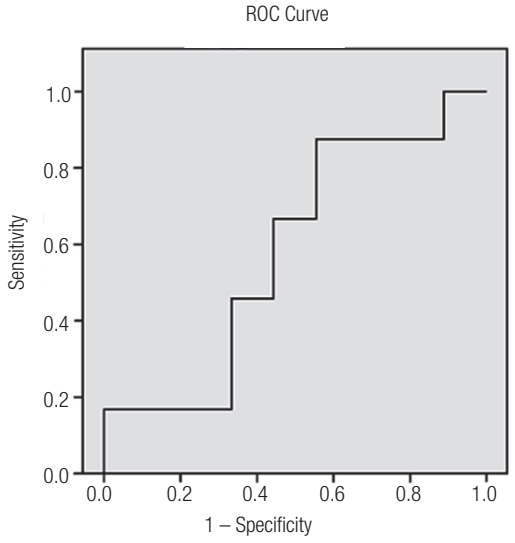

Figure 2. ROC plot to predict the presence of future cardiovascular risk in GDM group. The optimal vitamin D cut off point for predicting future cardiovascular risk was 10.4 ng/mL (AUC = 0.58) (MPV value indicating future cardiovascular risk was considered as 8.7 fl).

DISCUSSION

In this study, we demonstrated that there is a correlation between low 25(OH)D_3 level and high MPV in pregnant women with GDM at the first time.

GDM is a significant but frequently neglected problem for the future health of the mother. Women with a history of GDM have an increased risk of cardiovascular diseases. It is suggested that GDM is a risk factor for long-term cardiovascular morbidity independent of pre-pregnancy obesity, race, parity, and age in recent studies with a large cohort (25,26). Furthermore, it has been shown that during the intervening years after delivery the risk of early subclinical atherosclerosis starts before the onset of diabetes and the metabolic syndrome (27). Some studies have reported vascular endothelial dysfunction, increased serum levels of endothelial dysfunction, and inflammatory markers in women having an history of GDM but currently free from metabolic abnormalities (28). However, all pregnant women with complicated GDM do not have the same level of cardiovascular morbidity risk. In this study, it is argued that an increase in the risk of future cardiovascular morbidity in women with GDM might be associated with additional co-factors.

Circulating markers of systemic inflammation, such as C-reactive protein or interleukin-6, markers of endothelial dysfunction, such as E-selectin or vascular adhesion molecule-1, inhibitors of the fibrinolytic system, such as Plasminogen activator inhibitor-1, and markers of platelet dysfunction, such as MPV, have been studied as a predicting marker of future cardiovascular diseases risk (29-31). However, none of the aforementioned markers have a high sensitivity in predicting the risk of future cardiovascular disease in women with GDM. Our study was based on the increased MPV value's ability to predict the risk of future coronary disease.

It has been claimed that MPV is higher in pregnant women with GDM, and that high MPV could demonstrate an increase in the risk for current and future thrombotic complications (14,15). In our study, we observed higher but statistically insignificant MPV in pregnancies with GDM (p = 0.06). On the other hand, when considered together with the IGT and GDM group as well as the GMD group, there was a significant relationship between two groups (p = 0.04). This condition may be due to the small number of GDM patients when compared to the control group.

Platelet activity has been associated with acute vascular events. The use of anti-platelet agents is a class I recommendation for treatment and secondary prevention in patients with coronary artery disease (32). Although the precise biological pathways by which elevated MPV might influence the development or progression of cardiovascular disease are not completely understood, larger platelets are metabolically more active than smaller platelets. Recently, a large-scale meta-analysis showed that elevated MPV is associated with AMI mortality following myocardial infarction, as well as restenosis after coronary angioplasty (32). Based on

these data, researchers suggested that MPV is a potentially useful prognostic biomarker in patients with cardiovascular disease. But, there is not an absolute MPV value for predicting future cardiovascular risk. Various thresholds (i.e., ≥ 7.3 to ≥ 9.9 fL) have been used for defining high MPV. In our study, we want to evaluate the role of low $25(OH)D_3$ in predicting cardiovascular risk using a MPV cut-off, which was found in a national study. Based on this we accepted 8.7 fl. for the MPV cut-off value, which is a predicting value for moderate cardiovascular risk in Ekici and cols.'s study (24). According to the ROC curve analysis result, the optimal cut off points of $25(OH)D_3$ for predicting future cardiovascular risk was found to be 10.4 ng/mL (AUC = 0.58).

Similar to recent studies, our study showed a significant increase in prevalence of vitamin D deficiency in women with GMD when compared to the controls ($p < 0.01$) (12). There are several mechanisms proposed for explaining the association between vitamin D insufficiency and risk of GDM. It is suggested that a low serum vitamin D decrease in β-cell function, insulin sensitivity in pancreatic β-cells, and vitamin D insufficiency may lead to inadequate intracellular cytosolic calcium, which is essential for insulin-mediated intracellular processes and glucose regulation in peripheral cells (30). But, the effect of vitamin D deficiency on increased risk of cardiovascular disease in GDM has not been investigated extensively. Whereas some pathological changes associated with vitamin D deficiency, such as systemic inflammation, calcium storage in coronary artery, impaired endothelial function and platelet activation, may contribute to the increase in cardiovascular injury in GDM (9). We found that MPV values were significantly higher in the vitamin D deficient group than pregnant women with normal vitamin D levels in the GMD group ($p = 0.04$). However, the same relationship was not observed in pregnant women with normal glucose metabolism ($p = 0.9$).

There are two studies in literature investigating the relationship between MPV and vitamin D. In the first study, it is demonstrated that there is a strong association between a low $25(OH)D_3$ level and a high MPV in 438 healthy volunteers. In the second study, it is demonstrated that patients with primary ovarian insufficiency (43 patients) had high MPV and low $25(OH)D_3$ levels (17,33). Based on this data, researchers claimed that the low level of $25(OH)D_3$ could increase the risk of thrombosis and atherosclerosis in primary ovarian insufficiency. Although we used multiple different statistical methods, we did not find a relationship between $25(OH)D_3$ and MPV in pregnant women with normal glucose metabolism in our study.

This study has several limitations. First, the number of enrolled patients was inadequate for reflecting the general population. The aim of the initial study was to select normal and GDM women at the beginning, so the statistical evaluation could be more appropriate. However, during the period of the study, the number of pregnant women admitted to our clinic was not high enough for such a cross-sectional study. Second, the platelet indices have been shown to be sensitive to the differences in blood sample anticoagulation, storage temperature, and delays in processing. In particular, the time-dependent swelling of platelets in samples anticoagulated with EDTA can result in an artificial increase of MPV and misinterpretation of prothrombotic changes. It was demonstrated that, after the first hour of sampling, MPV values of EDTA samples were at least 9% higher than those of citrated samples (34). Although MPV measurement was performed within the first hour in our study, citrate was used as an anticoagulant so doubts about the EDTA might be unfounded. On the other hand if MPV evaluation is a simple, inexpensive, and widely available predicting test for cardiovascular risk, to use EDTA in research as a routine practice may be a reasonable approach. Thus, in a meta-analysis of 26 studies, EDTA was used in most of the studies, and it has been proposed that the EDTA-citrate difference should be ignored (35). Third, the level of $25(OH)D_3$ is affected by seasonal changes. Blood sampling for our study coincided with the summer and autumn period where the level of $25(OH)D_3$ is expected to be higher. Although we have shown that there was no significant difference in the duration of sun exposure between the groups, a one-year study period would be more appropriate to assess seasonal differences. As a result, further studies with a better design, multi-centered, and with a long study period are needed to validate our findings. Additionally, MPV is not the only indicator for future cardio vascular risk, and classic risk factors should not be ignored. The cut-off value of MPV that we used for ROC analysis is also not supported by other studies.

In summary, vitamin D deficiency may be a contributing factor to future risk of cardiovascular disease in pregnant women with GDM. Ensuring adequate levels of $25(OH)D_3$ in pregnant women with GDM may reduce the severity of injury created by hyperglycemia. It

is recommended that this important issue for the long-term health of pregnant women with GDM be investigated in future studies.

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