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RESEARCH ARTICLE

PLATELET PROFILE IN PREGNANT WOMEN WITH GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Objective: To evaluate and compare the platelet profile of pregnant women with gestational diabetes and normal pregnancy and to assess the changes in the platelet profiles of gestational diabetes patients before and after 8-10 days of their treatment. **Methods**: A prospective study was performed on 70 pregnant women between 24 – 28 weeks of their pregnancy: 30 cases with gestational diabetes and 40 healthy controls. The two groups were compared in terms of demographics and platelet parameters derived from complete blood counts and the effect of treatment on platelet parameters of gestational diabetes. **Results:** A significant difference was observed for mean platelet volume values between the gestational diabetes mellitus and normal pregnant groups ($p<0.0001$) and also between the mean platelet volume values in the gestational diabetes mellitus group before and after their treatment ($p<0.0001$). **Conclusion:** Elevated mean platelet volume can be used as an effective marker for the assessment of glycemic control in gestational diabetes mellitus.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (American Diabetes Association, 2014) and carries a 7-12-fold lifetime risk for the subsequent development of type 2 diabetes (Bellamy *et al.,* 2009). It is the most common metabolic complication of pregnancy affecting 4.6% to 14% of the pregnant population in India (Anjana *et al.,* 2011). Considering the gestational diabetes mellitus consequences of increased perinatal and maternal morbidity and mortality in addition to long-term complications, its accurate identification and treatment is of utmost importance (Grundy, 2012; Kosus *et al.,* 2012). Diabetes is an established risk factor for Cardiovascular disease; therefore, the subset of women with gestational diabetes mellitus who develop type 2 diabetes mellitus are at an increased risk of developing a cardiovascular disease in the future (American Diabetes Association, 2016). Altered platelet morphology and function have been reported in patients with diabetes mellitus (Poyhonen *et al.,* 2012). These changes may be associated with an increased risk of vascular disease and venous thromboembolism (Poyhonen *et al.,* 2012; Stein *et al.,* 2009). Close observation of women with gestational diabetes mellitus is essential to prevent complications of diabetic illnesses associated with hyperglycemia, which has a negative influence on all maternal systems and fetal homeostasis (Kakouros *et al.,* 2011).

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Hyperglycemia and insulin resistance increase platelet activation and activated platelets, in turn, have a higher thrombogenic potential (Strauss *et al.,* 2010). In a normal pregnancy, changes in platelet volume may be more sensitive than platelet numbers as a measure of altered platelet function (Erikci *et al.,* 2008). Platelet volumes are direct indicators of increased platelet synthesis (Strauss *et al.,* 2010). Platelet activity and aggregation potential can be estimated by measuring mean platelet volume as a part of complete blood count. Patients with high mean platelet volume values have larger platelets and can easily be identified during the routine hematological examination. Elevated mean platelet volume values are associated with larger and more active platelets and perceived as a new independent cardiovascular risk factor (Iyidir *et al.,* 2014). Hypercoagulability and vascular dysfunction cause micro thrombosis in placental bed vessels and placental infarction (Bozkurt *et al.,* 2006). Consequently, this generates an impairment in the fetomaternal circulatory system, which results in low placental perfusion and finally in fetal loss (Bozkurt *et al.,* 2006). Although normal pregnancy may result in the activation of primary hemostasis and coagulation, these issues have not been widely investigated in gestational diabetes. Mean platelet volume is a simple and cost-effective tool that could be used for predicting the possibility of impending acute events like myocardial infarction and cerebrovascular events (Desai *et al.,* 2013; Chu *et al.,* 2010) as well as chronic disorders such as type 2 diabetes mellitus. In this study, we aimed to assess the platelet parameters of pregnant women with gestational diabetes in comparison to the patients with normal glucose tolerance.

The objectives of this study are:

1. To evaluate and compare the platelet profile of pregnant women with gestational diabetes mellitus and normal pregnant women.
2. To assess the changes in the platelet profile of gestational diabetes mellitus patients before and after 8-10 days of their treatment.

MATERIALS AND METHODS

A prospective study was performed in the Department of Pathology and the Department of Obstetrics and Gynaecology on 70 pregnant women (30 gestational diabetes and 40 healthy controls) between July and September 2017, at a tertiary care teaching hospital. Following the approval of the Institutional Ethical Committee, the relevant information on demographic details and blood samples were collected from pregnant women at 24-28 weeks of gestation in the Out-Patient Department who visited our hospital for a routine check-up during their second trimester.

The procedure and importance of collecting the samples were explained to all participants in their own language. Cases diagnosed with hemoglobinopathy, chronic inflammatory disease, renal failure, cyanotic congenital heart diseases, pre-existing diabetes mellitus, preeclampsia as well as participants with a positive 50–gram Oral Glucose Challenge Test (OGCT) but negative 100-gram Oral Glucose Tolerance Test (OGTT) were excluded from both the study groups. All pregnant women who had normal medical histories before pregnancy were included in the study. Both the study groups were single-blinded. A peripheral venous blood sample was collected from the antecubital vein in plain tubes for testing the Fasting Blood Sugar (FBS) levels, Post- Prandial Blood Sugar (PPBS) levels and Glycosylated hemoglobin (HbA_{1c}) while subjecting them to an Oral Glucose Challenge Test (OGCT). The FBS, PPBS and HbA_{1c} were assessed using Beckman Coulter AU480. Simultaneously, venous blood collected in EDTA tubes were assessed for platelet parameters, as a part of complete blood count, using Beckman Coulter LH 780, 1-2h after collection. Controls were used on a regular basis to ensure the accuracy and precision of the instruments. Screening for Gestational Diabetes was done as per the American Diabetes Association (ADA) guidelines 2016 (American Diabetes Association, 2016). Pregnant women were diagnosed with gestational diabetes mellitus if: FBS $\geq$ 96mg/dL, PPBS $\geq$ 120 mg/dL and $HbA_{1c}\geq$6.5 % (48 mmol/mol) (Greer, 2009). The mean platelet volume reference range was determined as 7.5 – 10.5 Fl (Greer, 2009). The reference range for platelet count was 150,000 – 400,000/µL and for platelet distribution width was 15.6 – 17.5 % (Greer, 2009). Based on the level of hyperglycemia, the patients were put on suitable treatment. In these patients, haematological parameters were re-assessed after 8-10 days. Statistical analyses were performed using SPSS software version 24.0 for Windows Vista (SPSS Inc., Chicago, Illinois, USA). Data showing normal distribution of parameters were compared with student t-test. The relation of mean platelet volume with other complete blood count parameters was compared with Pearson correlation analysis and the relationship between two continuous variables, platelet count and mean platelet volume were assessed by linear regression analysis. All tests were two-sided with a 0.05 statistical significance level.

RESULTS

A total of 70 patients fulfilling the inclusion criteria were selected and divided into two groups. These included 40 (57.14%) normal pregnant women and 30 (42.86%) gestational diabetes women. The mean age of the gestational diabetes patients (29.2 years) was significantly higher than mean control age (23.9 years) with a significant difference and p=0.0002. The mean gravidity of the gestational diabetes mellitus patients was found to be higher than the controls but there was no significant change (p=0.62). The mean parity of gestational diabetes cases was higher than the control group but no significant change was observed. The mean Body Mass Index (BMI) of gestational diabetes mellitus patients (30.5 kg/m^2) was significantly higher than the control pregnant women (25.9 kg/m^2) and p=0.0003. Analysis of the data shows that the body mass indices and the number of parities were increased in parallel with the advancement of maternal age. When the two groups were compared for biochemical parameters, the mean Oral Glucose Load (OGL) results were 93.2 mg/dL and 179.8 mg/dL in the control and gestational diabetes mellitus groups, respectively. There was a significant difference between the two groups in terms of Oral Glucose Load results (p<0.0001).

The mean FBS results were 78.1 mg/dL and 125.2 mg/dL for the control and gestational diabetes mellitus groups respectively, with a significant difference and p<0.0001. The mean PPBS results were 115.9 mg/dL and 206.9 mg/dL for the control and gestational diabetes mellitus groups respectively, with a significant difference and p-value <0.0001 (Table 1). The mean HbA_{1c} results were 5.3% and 6.9% for the control and gestational diabetes mellitus groups respectively, with a significant difference and p-value <0.0001 (Table 1). The mean MPV values in the two groups were 8.9 and 10.8 fL, in the non-diabetic and gestational diabetes mellitus groups, respectively. A significant change was observed in the mean platelet volume values between the two groups (p <0.0001) (Table 1). The FBS values of the participants were well correlated with the mean platelet volume (r=0.511 and p<0.001) and the HbA_{1c} values also showed a correlation with the mean platelet volume values (r=0.483 and p<0.001).

Table 1. Demographic, clinical and laboratory results of the control and study groups

	Control group (n=40)	Gestational diabetes group (n=30)	
Parameters	Mean ± SD	Mean ± SD	p-value
Age (years)	23.9 ± 5	29.2 ± 6.3	0.0002*
Gravida (n)	1.9 ± 0.8	2 ± 0.9	0.625
Parity (n)	0.8 ± 0.6	0.8 ± 0.8	0.727
BMI (kg/m^2)	25.9 ± 5.4	30.5 ± 4.2	0.0003*
OGL (mg/dL)	93.2 ± 18.8	179.8 ± 53.8	<0.0001*
FBS (mg/dL)	78.1 ± 10.2	125.2 ± 42.4	<0.0001*
PPBS (mg/dL)	115.9 ± 12.6	206.9 ± 73.8	<0.0001*
HbA_{1c} (%)	5.3 ± 0.5	6.9 ± 1.7	<0.0001*
RBC count (million)	4.1 ± 0.4	4.2 ± 0.5	0.182
Hemoglobin (g/dL)	12.0 ± 4.1	11.9 ± 1.1	0.849
Hematocrit (%)	33.4 ± 3.6	34.9 ± 3.2	0.079
RDW (%)	15.1 ± 2.1	15.2 ± 2.6	0.842
WBC count ($x10^3$/mL)	11.0 ± 1.9	9.8 ± 2.1	0.093
Platelet count ($x10^3/\mu L$)	254.8 ± 50.1	234.2 ± 65.9	0.141
MPV (fl)	8.9 ± 0.9	10.8 ± 1.1	<0.0001*
PDW (%)	14.5 ± 2.9	15.4 ± 1.5	0.881

BMI: body-mass index, OGL: oral glucose load, FBS: fasting blood glucose, PPBS: post-prandial blood glucose, HbA1c: glycosylated hemoglobin, RDW: red cell distribution width, WBC: white blood cell, MPV: Mean platelet volume, PDW: platelet distribution width; *p<0.05: Statistically significant difference between normal OGL and GDM group; SD: standard deviation; Student-t test

Table 2. Hematological changes in the Gestational diabetes cases after 8-10 days of their treatment

	GDM pregnant women (n=30)	GDM pregnant women following 8=10 days of their treatment (n=30)	
Parameters	Mean ± SD	Mean ± SD	p-value
Platelet count ($x10^3/\mu L$)	234.2 ± 65.9	244.2 ± 67.3	0.424
MPV (fl)	10.8 ± 1.1	9.3 ± 1.0	<0.0001*
PDW (%)	15.4 ± 1.5	15.0 ± 2.6	0.600
WBC count ($x10^3$/mL)	9.8 ± 2.1	10.2 ± 1.5	0.276
RBC count ($x10^6$/mL)	4.2 ± 0.5	4.1 ± 0.5	0.225
Hemoglobin (g/dL)	11.9 ± 1.1	11.6 ± 1.2	0.210
RDW (%)	15.2 ± 2.6	15.3 ± 2.2	0.751
Hematocrit (%)	34.9 ± 3.2	34.7 ± 3.5	0.744

(GDM: gestational diabetes mellitus, MPV: mean platelet volume, PDW: platelet distribution width, WBC: white blood cell, RDW: red cell distribution width) *p<0.05: Statistically significant difference is seen between normal Oral glucose load and gestational diabetes group.

The mean platelet counts were slightly higher in the control (254,800/µL) than in the gestational diabetes group (234,200/µL) but not statistically significant (p=0.141). The mean platelet distribution width of the gestational diabetes mellitus and control groups are 14.6% and 15.4% respectively, with no significant difference between the two (p=0.881). Patients with high mean platelet volume had a lower platelet count (Figure 1).

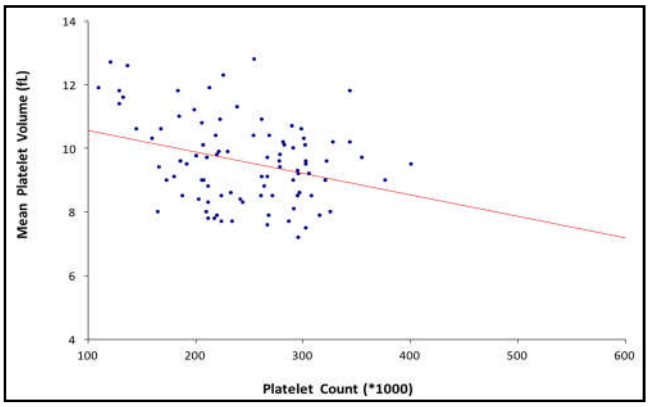

Figure 1. Correlation between platelet count and mean platelet volume

The mean platelet volume was well correlated with the platelet count (r=0.319, p<0.001) and the platelet distribution width (r=0.056, p<0.001). When the two groups were compared for other hematological parameters: RBC count, hemoglobin, hematocrit, RDW, WBC count, the values were similar with no significant change between the two groups (Table 1). The mean MPV value was lower while on treatment (9.3 fL) than before (10.8 fL) with a significant change (p < 0.0001) (Table 2). The platelet count was slightly lower after their treatment (2.44 lac) than before (2.34 lac) but no statistical significance was noted (p=0.424). The platelet distribution width of the patients changed from 15.4% before treatment to 15% after their treatment with no significant change (p=0.6). The red blood cell count, haematocrit, haemoglobin and white blood cell count results were similar before and after their treatment with no significant change.

DISCUSSION

Gestational diabetes mellitus is a significant but frequently neglected problem regarding the future health of the mother. Platelets play an important role in the normal homeostasis of the body and mean platelet volume is an indicator for their normal function. The relationship of gestational diabetes mellitus with platelet profile was carried out in many studies to assess if mean platelet volume could be used as a marker for a future cardiovascular risk.

The mean maternal age of the gestational diabetes pregnant women in this study is 29.2 years, while that in the study done by Sak *et al.* (2012) was 31.2 years, Kosus *et al* (2012) showed mean age of 31.2 years and the study done by Abel-Rahman *et at.* (2012) showed mean age of 31.8 years, all being significantly higher than the mean age of the healthy controls (p=0.0002). The mean age of the gestational diabetes mellitus patients in our study is much lower than the studies mentioned above which raise profound concern. As the risk of gestational diabetes becomes significantly and progressively increased from 25 years onwards, a maternal age of 25 years should be adopted as a cut-off instead of 35 or 40 years as a risk factor for the development of gestational diabetes mellitus (Lao *et al.,* 2006). The earlier realization of gestational diabetes and its effective management will greatly reduce the morbidity and mortality in the mother and the fetus.

The body mass indices and the number of parities are increased in parallel with the advancement of maternal age which is similar to the study done in Turkey by Sak M *et al.* (2012). Our study shows a significant difference (p=0.0003) in the body mass index values of gestational diabetes cases (mean=30.5 kg/m^2) and controls (mean= 25.9 kg/m^2) which is in accordance with the study done by Sak *et al*. (2012). This finding highlights the need for careful recognition of risk factors such as a booking weight ≥ 70kg and a BMI ≥ 25 kg/m^2. This information is also important whilst counselling women planning for pregnancy. Also, promotion of physical activity and healthy eating among women of reproductive age should be popularised.

The mean Oral glucose load value of the gestational diabetes cases in our study is 179.8 mg/dL and p<0.001 while that obtained in the study done by Kosus *et al.* (2012) was 172.1mg/dL and p<0.001, the mean oral glucose load obtained in the study by Cetlik *et al.* (2016) was 104.06mg/dL and p<0.001, while it was 171.8mg/dL and (p<0.05) in the study done by Abel-Rahman *et al.* (2012). The mean FBS of the gestational diabetes mellitus group in our study is 125.2 mg/dL with significant difference with the control group (p<0.001) while that of Guducu *et al.* (2015) was 96.81 mg/dL and p=0.02 which is very low compared to our mean FBS. The mean oral glucose load and the mean FBS in our study are high compared to the studies mentioned above probably due to lack of awareness about adopting proper lifestyle measures such as diet control and exercise in this pregnant population, leading to poor glycemic control. The mean MPV of the gestational diabetes mellitus cases in our study is 10.8 fL and p<0.001 as compared to 8.9 fL and p=0.001 by Sak *et al* (2012), 8.67 fL and p<0.05 by Kosus *et al.* (2012) and 8.71 fL and p<0.05 by Abel-Rahman SM *et al.* (2012).

This increased platelet volume in gestational diabetes mellitus patients may be attributed to:

- Accelerated platelet production due to which younger platelets with higher volume increase in the peripheral circulation (Stein *et al.,* 2009).
- Isosmotic swelling of the platelets due to the raised level of blood glucose or glucose metabolites (AJMS, 2009).

In our study, the increased mean platelet volume can be attributed to high blood glucose levels (mean FBS= 125.2mg/dL). The relationship of mean platelet volume with platelet count is found to be inverse in a linear regression with r=0.319 in our study while it was r=0.105 in Kosus *et al* (Kosus *et al.,* 2012) and r=0.355 in study done by Sak *et al.* (2012). However, the present study and the studies done by the mentioned authors (Kosus *et al.,* 2014; Bozkurt *et al.,* 2006; Sak *et al.,* 2012; Abel-Rahman *et al.,* 2012) did not find a significant relationship between the two parameters. Only the study done by Erikci *et al.* (2010) showed a significant relationship ($p<0.006$). The mean platelet distribution width of the gestational diabetes mellitus cases in our study is 15.4% as compared to 18.2% obtained in the study by Sak *et al.* (2012), 15.9% obtained in the study done by Kosus *et al* (2010) and 16.0% in the study done by Abel-Rahman *et al.* (2012). The correlation between mean platelet volume and platelet distribution width is well established in our study, with r=0.056, $p<0.001$ and is similar to that obtained in their study Sak M *et al* with r=0.404.

The mean HbA_{1c} of the gestational diabetes mellitus cases in the present study is 6.9% ($p<0.001$) as compared to 5.7% and $p<0.001$ in Sak M *et al.* (2012). This finding was expected. On comparison of the gestational diabetes mellitus and healthy pregnant groups, our study reveals that mean platelet volume and HbA_{1c} are increased in gestational diabetes mellitus ($p<0.001$) and is in accordance with the results obtained by Sak M *et al.* (2012). This identification suggests that mean platelet volume can be used as a marker for the follow-up of the gestational diabetes mellitus patients. In our study, mean platelet volume values were found to be higher initially (10.8 fL), but with the decrease in blood glucose, a significant decrease (9.3 fL) in mean platelet volume values was also observed ($p<0.001$). This may be attributed to the isosmotic swelling of the platelets due to the raised level of blood glucose or glucose metabolites (AJMS, 2009) such that with the achievement of glycemic control (while they were put on treatment) the mean platelet volume reduced with the falling blood glucose levels. Only 23 out of the 30 patients (77%) with gestational diabetes mellitus showed a correlation of mean platelet volume with FBS and HbA_{1c}. Therefore, in the remaining 7 patients (23%) factors like the number of pregnancies, the age of the mother, gestational age, gravidity, obesity, and lifestyle, must have possibly influenced the increase in mean platelet volume. However, there is no significant change in other platelet parameters namely, platelet count and platelet distribution width in the current study, after their blood glucose was normalized. The identification of a high mean platelet volume in gestational diabetes mellitus patients suggests that mean platelet volume may be used as a reliable marker for the follow-up of these patients. The modifications in glycemia undetectable by standard clinical laboratory methods can be reflected via alterations in platelet parameters. With periodic assessment of platelet profiles in gestational diabetes mellitus, we strongly believe that their observation and treatment will improve, which will subsequently decrease the maternal and fetal morbidity and mortality.

Conclusion

The present study shows that increased levels of mean platelet volume can be used as an effective marker for the assessment of glycemic control in gestational diabetes during pregnancy. The complications in these patients could not be followed up due to time constraint. Awareness and screening programmes at regular intervals is necessary to identify future risk of cardiovascular disease in pregnant women with gestational diabetes mellitus.

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Conflict of Interests: There are no conflicts of interest.

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