ORIGINAL ARTICLE

EVALUATION OF THE SIMPLE HEMATOLOGIC MARKERS IN PATIENTS WITH GESTATIONAL DIABETES MELLITUS: A CASE-CONTROL STUDY

Gestasyonel Diabetes Mellituslu Hastalarda Basit Hematolojik Belirteçlerin Değerlendirilmesi: Vaka-Kontrol Çalışması

Eren PEK[1] , Fatma BEYAZIT[1]

[1]Çanakkale Onsekiz Mart University Faculty of Medicine Department of Obstetrics and Gynecology

Eren PEK, Dr. Öğr. Ü. (0000-0003-1060-9613)
Fatma BEYAZIT, Doç. Dr. (0000-0002-0667-6090)

İletişim:
Dr. Öğr. Ü. Eren PEK
Çanakkale Onsekiz Mart University Faculty of Medicine Department of Obsterics and Gynecology

e-mail: drerenpek@hotmail.com

Geliş tarihi/Received: 27.01.2021
Kabul tarihi/Accepted: 04.08.2021
DOI: 10.16919/bozoktip.869129

Bozok Tıp Derg 2021;11(3):x-x
Bozok Med J 2021;11(3):x-x

ABSTRACT

Objective: Gestational diabetes mellitus (GDM) is defined as various degrees of glucose intolerance that begins or is first detected during second or third trimester of pregnancy. In order to prevent serious maternal and/or neonatal outcomes, early diagnosis and adequate treatment strategies are of great importance. Simple hematologic parameters such as mean platelet volume (MPV), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have increasingly been reported as measures of presence and severity of GDM. This study aimed to determine whether there is an association between these parameters and the presence of GDM

Material and Methods: A total of 78 GDM patients and 89 age- and gestational-age-matched pregnant controls were studied. MPV, RDW, NLR and PLR values in all patients were calculated and recorded from complete blood cell counts.

Results: For GDM patients, the mean MPV, NLR, PLR and RDW values were 8.8±1.0, 3.8±2.3, 120.6±42.9, and 15.3±2.6 respectively; for healthy pregnant controls, the values were 8.6±0.8, 3.5±2.1, 130.6±40.8, and 14.1±1.8 respectively. Although only MPV and RDW levels of GDM patients were significantly higher compared with healthy controls, no statistically significant difference was found between both study groups in respect to PLR and NLR.

Conclusion: Mean platelet volume and RDW but not NLR and PLR, which are automatically calculated from complete blood count parameters plays important predictive roles in GDM.

Keywords: *Gestational Diabetes Mellitus; Mean Platelet Volume; Red Cell Distribution Width; Platelet-To-Lymphocyte Ratio; Neutrophil-To-Lymphocyte Ratio*

ÖZET

Amaç: Gestasyonel Diabetes Mellitus (GDM) gebeliğin ikinci veya üçüncü trimesterinde başlayan veya tanı konan değişik derecedeki glukoz intoleransı olarak tanımlanır. Ciddi maternal ve/veya neonatal sonuçları önlemek için erken tanı ve uygun tedavi yaklaşımları büyük önem arz etmektedir. Ortalama platelet hacmi (MPV), kırmızı küre dağılım genişliği (RDW), nötrofil-lenfosit oranı (NLO) ve platelet –lenfosit oranı (PLO) gibi basit hematolojik parametrelerin GDM varlığı ve şiddetinin bir ölçütü olarak kullanılabileceği belirtilmiştir. Bu çalışmanın amacı bu parametreler ile GDM varlığı arasında bir ilişkinin var olup olmadığının belirlenmesidir.

Gereç ve Yöntemler: Bu çalışmaya 78 GDM hastası ile gestasyonel yaş uyumlu 89 gebe kontrol dahil edilmiştir. MPV, RDW, NLO ve PLO değerleri tüm hastalar için tam kan sayımından hesaplanmış ve kaydedildi.

Bulgular: GDM hastaları için ortalama MPV, NLO, PLO ve RDW değerleri sırasıyla 8,8±1,0, 3,8±2,3, 120,6±42,9 ve 15,3±2,6; kontrol grubu için ise sırasıyla 8,6±0,8, 3,5±2,1, 130,6±40,8 ve 14,1±1,8 idi. Her ne kadar MPV ve RDW değerleri GDM hastalarında kontrol grubu ile kıyaslandığında belirgin yüksek saptanmış ise de, NLO ve PLO değerleri her iki grupta benzer idi.

Sonuç: Tam kan sayımından otomatik olarak hesaplanan MPV ve RDW değerlerinin GDM hastalarında yüksek olarak saptanması bu parametrelerin GDM'de prediktif rolleri olabileceğini düşündürtmektedir.

Anahtar Kelimeler: *Gestasyonel Diabetes Mellitus; Ortalama Trombosit Hacmi; Kırmızı Küre Dağılım Genişliği; Platelet –Lenfosit Oranı; Nötrofil-Lenfosit Oranı*

INTRODUCTION

Gestational diabetes mellitus (GDM) is a prediabetic disease state, recognized during pregnancy and is characterized by insulin resistance (IR) and inadequate insulin compensation (1). Patients with GDM usually do not present any significant clinical symptom, for this reason GDM screening in the second trimester has become a routine prenatal approach in pregnant women. Although a majority of GDM patients do not experience glucose intolerance during the postnatal period, it must be noted that these patients have an increased lifetime risk of type 2 diabetes mellitus and overt cardiovascular disease (2). Therefore, early identification and appropriate interventions are crucial in order to prevent the progression of undesirable consequences. In this context, it is not surprising to see extensive researches focusing on the prediction of GDM by several methods in early pregnancy.

The presence of low-grade inflammatory response and oxidative stress in which leucocytes and reactive oxygen species (ROS) play a key role, is the culprit of GDM pathophysiology. The main pro-inflammatory cytokines such as IL-8, TNF-α and IL-6, which are common cause of primary inflammatory response and elevated total oxidant status with disulfide/total thiol and disulfide/native thiol ratios are found to be elevated in GDM patients that support dysregulation of the biological system during disease process (3-5). Mean platelet volume (MPV), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are simple and easy to calculate hematologic indices that have been demonstrated to show inflammatory status and disease activity in a number of disorders such as GDM (6-8). Unfortunately, these findings were inconsistent across studies, many of which were limited by relatively small sample size and by the lack of replication. Thus, there are still no clinically defined diagnostic characteristics with respect to complete blood cell counts (CBC) which can discriminate GDM from non-GDM pregnancy. The aim of the present study is therefore to investigate the diagnostic capacity of MPV, RDW, PLR and NLR in gestational diabetic and normal pregnant women.

MATERIALS AND METHODS

A total of 78 pregnant women with GDM, at 26.3±5.6 weeks gestation, and 89 pregnant controls without any complaints and matched for gestational age were found to be eligible for this study. Patients were recruited from the outpatient gynecology and obstetrics clinics of the Çanakkale Onsekiz Mart University Faculty of Medicine medical center. All pregnant women included in this study underwent routine GDM screening in 24 and 28 weeks of gestation with the 75 g oral glucose tolerance test (OGTT) and GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria (fasting glucose concentration ≥92 mg/dl, 1-h concentration of glucose ≥180 mg/dl, and 2-h concentration of glucose ≥153 mg/dl.) (9). Pregnant women with chronic systemic illnesses, preeclampsia, multiple pregnancies, pre-existing glucose intolerance with or without a history of insulin or oral antihyperglycemic agents, pregnancy-induced hypertension, acute or chronic inflammation and active cigarette smokers were not included to the present study.

After database access was granted by the management of the Çanakkale Onsekiz Mart University Faculty of Medicine Center, the following clinical, laboratory and demographic data from the Çanakkale Onsekiz Mart University Faculty of Medicine Hospital Information and Management System (HIMS) were recorded for each patient: age, gestational age, gravidity, parity, and complete blood cell count parameters including hemoglobin (Hgb), white blood cell (WBC), neutrophil count, lymphocyte count, MPV, and RDW. NLR and PLR were calculated for each study participant from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count and by dividing the platelet count by the lymphocyte count respectively.

All blood specimens were gathered without the use of any anticoagulant from the antecubital vein after 12 hours fasting and all CBC calculations were carried out in the hematology laboratory of Çanakkale Onsekiz Mart University Faculty of Medicine medical center using the same Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer.

This study is conducted in accordance with Helsinki Declaration and ethical approval was granted from institutional ethical board to perform study protocol.

Bozok Tıp Derg 2021;11(3):x-x
Bozok Med J 2021;11(3):x-x

Statistical analysis

To analyse statistical data Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) software was used. Continuous data were tested for normality with the Kolmogorov-Smirnov test. Continuous data was presented as means ± Standard deviation or medians [minimum–maximum], as appropriate. Mann-Whitney U test was used to compare the data that was not normally distributed. Proportions were compared using the student t test and all p values <0.05, considered statistically significant.

RESULTS

A case–control study design was used in this study to retrospectively select participants in the GDM case group and non-diabetic healthy pregnant control group from the described population. Clinical and demographic characteristics of GDM patients and healthy controls are summarized in Table 1. The patient and control groups were similar for age, gestational age, gravidity and parity. Mean MPV values of GDM patients and controls were 8.8±1.0 and 8.6±0.8 respectively. This difference was found to be statistically significant (p=0.015). Mean RDW values of GDM patients and controls were 15.3±2.6 and 14.1±1.8 respectively. This difference was also found to be significant between groups (p=0.001). No statistically significant difference was observed in both groups in respect to NLR and PLR values (Table 2).

DISCUSSION

The present study revealed that although GDM patients have higher MPV and RDW levels compared with normal pregnancies, NLR and PLR were similar between two groups.

Mean platelet volume is a precise measurement of the dimension of platelets that provides information on platelet activation and velocity. It can either decrease or increase depending on the acuteness and severity of the inflammatory process and generally assessed by studies in various patient groups including diabetes mellitus (DM), appendicitis, hyperemesis gravidarum, pancreatitis, ulcerative colitis, Familial Mediterranean Fever, cardiovascular and cerebrovascular diseases (10-15). Studies focusing on the association between GDM and MPV initially started from the demonstration of the enhanced platelet activity in DM in which higher MPV levels were found to be independently related to DM. This association was not only found to be related with the presence of DM but also the severity of DM (10). In this context, several studies highlighted the diagnostic importance of MPV in GDM patients. Iyidir et al. showed increased levels of MPV in patients with GDM (16). Moreover, plasma glucose values and glucose area under the receiver operating characteristic curve (AUROC) were found to be positively related with 3rd trimester MPV levels. This finding was further supported by Baldane et al. and Colak et al. in which elevated MPV levels in GDM patients were demonstrated successfully (17,18). Based on these findings GDM can be regarded as a prothrombotic state with an elevated platelet activity and the possible pathophysiologic mechanisms behind this altered platelet morphology could be through increased glucose levels and IR in GDM patients (19). The intimate association between MPV and IR has been a subject of considerable investigation among researchers. In a large cross-sectional study by Muscari et al. MPV values were found to be linked with subcutaneous abdominal fat tissue, fasting blood glucose and tended to be higher in the subjects with a greater prevalence of hepatic steatosis and higher Homeostasis Model Assessment (HOMA) index (6). In

Table 1. Demographic and clinical characteristics of study population.

	Gestational Diabetes Mellitus (n=78)	Healthy pregnant controls (n=89)	p
Age (year)	30.7±5.2	29.0±4.5	0.052
Parity	1 (1-4)	2 (1-4)	0.155
Gestational age (week)	26.3±5.6	27.9±4.1	0.143
Glucose (mg/dl)	107.9±24.2	76.9±4.9	<0.001

Bozok Tıp Derg 2021;11(3):x-x
Bozok Med J 2021;11(3):x-x

Table 2. Baseline hematologic values of GDM patients and healthy pregnant controls.

	Gestational Diabetes Mellitus (n=78)	Healthy pregnant controls (n=89)	p
Hemoglobin (g/dL)	12.0±1.4	12.4±1.2	0.065
WBC (mm^3 $\times10^3$)	10.0±2.5	9.8±2.7	0.665
Platelet (mm3 $\times10^3$)	244.4±65.6	260.4±58.3	0.097
MPV (fL)	8.8±1.0	8.6±0.8	0.015
RDW (%)	15.3±2.6	14.1±1.8	0.001
Neutrophil (mm^3 $\times10^3$)	7.1±2.5	6.8±2.5	0.559
Lymphocyte (mm^3 $\times10^3$)	2.2±1.0	2.1±0.7	0.394
NLR	3.8±2.3	3.5±2.1	0.485
PLR	120.6±42.9	130.6±40.8	0.128

WBC, white blood cell; MPV, mean platelet volume; RDW, red cell distiribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

accordance, Coban et al revealed a significantly higher MPV values in their diabetic patient cohort compared with control (20). Contrary to these findings Erdogan et al. compared CBC parameters in GDM patients and found no significant difference between GDM patients and controls in terms of MPV (21). In our study, despite the similar platelet counts in both study groups, we found that MPV levels were elevated in GDM patients suggesting the production of larger platelets with increased platelet turnover due to a possible trigger of insulin.

Neutrophil to lymphocyte ratio and PLR are considered to be biological inflammatory indicators and reported to have strict associations with coronary heart diseases, inflammatory bowel disease, DM and tumoral conditions (22-25). Both of these parameters are simple, cheap, easy calculable and convenient biological indicators of systemic inflammation. Subclinical inflammation and IR are the two major pathophysiological mechanisms of DM and it is not surprising to find altered NLR and PLR levels in GDM. In a recent study by Liu et al. NLR and PLR were found to be elevated in GDM patients and both of these parameters were suggested to be independent variables for predicting GDM in pregnancy (7). Similarly, in a study by Yilmaz et al. in which 42 patients with GDM and 68 normoglycemic pregnant women were investigated, it has been demonstrated that NLR was significantly higher in patients with GDM (26). In contrast to these studies, the result of the present study did not show significant differences among the study groups. Similar to our findings, Sargın et al. also found no significant difference between GDM patients and controls in respect to NLR and PLR levels (27). Fashami et al demonstrated similar NLR values in both GDM patients and controls discouraging the use of this parameter in predicting GDM (28).

Although there is limited data on the association between RDW and GDM, we found a statistically significant increase in RDW levels in GDM patients. RDW, which is routinely calculated by most complete blood cell count analyzers, quantifies variability in the size of circulating red blood cells (RBCs) with decreased values representing greater homogeneity in red blood cell sizes (29). Although, the common use of RDW is to distinguish anemia etiologies (either microcytic anemia or macrocytic), recently it has been suggested that RDW levels may be altered by various clinical disease conditions such as inflammation, malignant biliary obstruction, cardiovascular disease, hemolysis and chronic renal failure (29-31). Furthermore, RDW is reported to be associated with a substantial increase in mortality in DM patients and the mechanism of this increase is not clear and possibly related to rapid erythrocyte elimination and increased oxidative stress similarly to other forms of DM. Although no significant association was found in respect to RDW levels between GDM patients and pregnant women, in the study of Erdogan et al, Sahbaz et al and Yildiz et al. have studied RDW in GDM patients and reported

significantly higher levels of RDW in GDM patients compared with healthy pregnant controls (8,21,32).

The relatively small sample size and retrospective design are the major limitations of the present study. Moreover, due to this retrospective nature, we do not have remarkable data on some hormonal, metabolic and demographic parameters such as body mass index, insulin, inflammatory and oxidative stress markers and how MPV, NLR, PLR and RDW changed after glycemic control was achieved during pregnancy. Thus, we also accept that revealing the associations between these simple hematologic parameters and adverse pregnancy outcomes would have been noteworthy.

CONCLUSION

MPV and RDW can be a potential marker in the early diagnostics of GDM. The possible effect of this finding on perinatal and fetal outcomes and its potential role in the selection of treatment modality for GDM needs to be further determined.

REFERENCES

1. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primers. 2019;5(1):47.

2. Retnakaran R. Glucose tolerance status in pregnancy: a window to the future risk of diabetes and cardiovascular disease in young women. Curr Diabetes Rev. 2009;5(4):239-44.

3. Amirian A, Mahani MB, Abdi F. Role of interleukin-6 (IL-6) in predicting gestational diabetes mellitus. Obstet Gynecol Sci. 2020;63(4):407-16.

4. Cakina S, Aydın B, Beyazit F. Evaluation of thiol/disulfide homeostasis in patients with gestational diabetes mellitus. Gynecol Endocrinol. 2020 Nov;36(11):1006-9.

5. Mohammed A, Aliyu IS. Maternal serum level of TNF-α in Nigerian women with gestational diabetes mellitus. Pan Afr Med J. 2018 Dec 28; 31:250

6. Muscari A, De Pascalis S, Cenni A, Ludovico C, Castaldini N, Antonelli S et al. Determinants of mean platelet volume (MPV) in an elderly population: relevance of body fat, blood glucose and ischaemic electrocardiographic changes. Thromb Haemost. 2008;99(6):1079-84.

7. Liu W, Lou X, Zhang Z, Chai Y, Yu Q. Association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume with the risk of gestational diabetes mellitus. Gynecol Endocrinol. 2021 Feb;37(2):105-7.

8. Sahbaz A, Cicekler H, Aynioglu O, Isik H, Ozmen U. Comparison of the predictive value of plateletcrit with various other blood parameters in gestational diabetes development. J Obstet Gynaecol. 2016;36(5):589-93.

9. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676-82.

10. Shah B, Sha D, Xie D, Mohler ER 3rd, Berger JS. The relationship between diabetes, metabolic syndrome, and platelet activity as measured by mean platelet volume: the National Health And Nutrition Examination Survey, 1999-2004. Diabetes Care. 2012;35(5):1074-8.

11. Beyazit Y, Sayilir A, Torun S, Suvak B, Yesil Y, Purnak T et al. Mean platelet volume as an indicator of disease severity in patients with acute pancreatitis. Clin Res Hepatol Gastroenterol. 2012;36(2):162-8.

12. Beyazit F, Öztürk FH, Pek E, Ünsal MA. Evaluation of the hematologic system as a marker of subclinical inflammation in hyperemesis gravidarum: a case control study. Ginekol Pol. 2017;88(6):315-9.

13. Chang HY, Hsu LW, Lee CH, Lin CC, Huang CW, Chen PW, et al. Impact of Platelet Volume on the Clinical Outcomes of Patients with Acute Coronary Syndrome. Acta Cardiol Sin. 2019;35(6):563-70.

14. Nishinaka T, Yamazaki Y, Niwa A, Wake H, Mori S, Yoshino T et al. Alterations of lymphocyte count and platelet volume precede cerebrovascular lesions in stroke-prone spontaneously hypertensive rats. Biomarkers. 2020;25(3):305-13

15. Bakan A, Oral A, Alışır ES, Sasak KG, Elçioğlu ÖC, Demirci R et al. Assessment of Mean Platelet Volume in Patients with AA Amyloidosis and AA Amyloidosis Secondary to Familial Mediterranean Fever: A Retrospective Chart - Review Study. Med Sci Monit. 2019; 25:3854-9.

16. Iyidir OT, Degertekin CK, Yilmaz BA, Toruner FB, Akturk M, Arslan M. Elevated mean platelet volume is associated with gestational diabetes mellitus. Gynecol Endocrinol. 2014;30(9):640-3

17. Baldane S, Ipekci SH, Kebapcilar A. Relationship Between Insulin Resistance and Mean Platelet Volume in Gestational Diabetes Mellitus. J Lab Physicians. 2015;7(2):112-5.

18. Colak E, Ozcimen EE, Ceran MU, Tohma YA, Kulaksızoglu S. Role of mean platelet volume in pregnancy to predict gestational diabetes mellitus in the first trimester. J Matern Fetal Neonatal Med. 2019;1-6.

19. Buchanan TA, Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? Diabetes Care. 2007;30 Suppl 2: S105-11.

20. Coban E, Bostan F, Ozdogan M. The mean platelet volume in subjects with impaired fasting glucose [published correction appears in Platelets. Platelets. 2006;17(1):67-9.

21. Erdoğan S, Ozdemir O, Doğan HO, Sezer S, Atalay CR, Meriç F et al.

Liver enzymes, mean platelet volume, and red cell distribution width in gestational diabetes. Turk J Med Sci. 2014;44(1):121-5.

22. Saheb Sharif-Askari F, Saheb Sharif-Askari N, Guella A, Alabdullah A, Bashar Al Sheleh H, Maher Hoory AlRawi A et al. Blood Neutrophil-to-Lymphocyte Ratio and Urine IL-8 Levels Predict the Type of Bacterial Urinary Tract Infection in Type 2 Diabetes Mellitus Patients. Infect Drug Resist. 2020; 13:1961-70.

23. Torun S, Tunc BD, Suvak B, Yildiz H, Tas A, Sayilir A et al. Assessment of neutrophil-lymphocyte ratio in ulcerative colitis: a promising marker in predicting disease severity. Clin Res Hepatol Gastroenterol. 2012;36(5):491-7.

24. Mertoglu C, Gunay M. Neutrophil-Lymphocyte ratio and Platelet-Lymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. Diabetes Metab Syndr. 2017;11 Suppl 1:S 127-31.

25. Wang H, Ding Y, Li N, Wu L, Gao Y, Xiao C et al. Prognostic Value of Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, and Combined Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Stage IV Advanced Gastric Cancer. Front Oncol. 2020; 10:841

26. Yilmaz H, Celik HT, Namuslu M, Inan O, Onaran Y, Karakurt F et al. Benefits of the neutrophil-to-lymphocyte ratio for the prediction of gestational diabetes mellitus in pregnant women. Exp Clin Endocrinol Diabetes. 2014;122(1):39-43.

27. Sargın MA, Yassa M, Taymur BD, Celik A, Ergun E, Tug N. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios: are they useful for predicting gestational diabetes mellitus during pregnancy? Ther Clin Risk Manag. 2016; 12:657-65.

28. Fashami MA, Hajian S, Afrakhteh M, Khoob MK. Is there an association between platelet and blood inflammatory indices and the risk of gestational diabetes mellitus? Obstet Gynecol Sci. 2020;63(2):133-40.

29. Paliogiannis P, Zinellu A, Mangoni AA, Capobianco G, Dessole S, Cherchi PL et al. Red blood cell distribution width in pregnancy: a systematic review. Biochem Med (Zagreb). 2018;15;28(3):030502.

30. Beyazit Y, Kekilli M, Ibis M, Kurt M, Sayilir A, Onal IK et al. Can red cell distribution width help to discriminate benign from malignant biliary obstruction? A retrospective single center analysis. Hepatogastroenterology. 2012;59(117):1469-73.

31. Katsaros M, Paschos P, Giouleme O. Red cell distribution width as a marker of activity in inflammatory bowel disease: a narrative review. Ann Gastroenterol. 2020;33(4):348-54.

32. Yildiz S, Üçler R, Alay M, Ekici EB. Which hemogram parameter is more cautionary in euthyroid patients with gestational diabetes mellitus. East J Med. 2016; 21:162-7.