Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI: 10.38136/jgon.806257

Normal Glisemik ve Gestasyonel Diyabetli Hastalarda İlk İki Trimester Boyunca Hemogram Parametrelerindeki Progresif Değişimlerin Karşılaştırılması ve Bu Endekslerin Gestasyonel Diyabetes Mellitusu Öngörme Yetenekleri

Comparison of the Progressive Changes in Hemogram Parameters of Normal Glycemic and Gestational Diabetic Patients Throughout the First Two Trimesters and Predictive Ability of These Indices for Gestational Diabetes Mellitus

Pelin AYTAN [1] Orcid ID:0000-0002-4213-1565
Seyran BOZKURT BABUŞ [2] Orcid ID:0000-0001-9503-2862
Özde SAKARYA [3] Orcid ID:0000-0002-0626-2015
Revan Sabri ÇİFTÇİ [3] Orcid ID:0000-0003-2560-3142
Kasım AKAY [3] Orcid ID:0000-0002-6098-2259
Hakan AYTAN [3] Orcid ID:0000-0002-2553-7715

[1] Mersin University Faculty of Medicine, Department of Hematology, Mersin, Turkey
[2] Mersin University Faculty of Medicine, Department of Emergency Medicine, Mersin, Turkey
[3] Mersin University Faculty of Medicine, Department of Obstetrics and Gynecology, Mersin, Turkey

ÖZ

Amaç: Gebeliğin ilk trimesterindeki hematolojik endekslerin gestasyonel diyabetes mellitusun (GDM) öngörülmesindeki rollerinin araştırılması ve ilk iki trimesterde bu parametrelerdeki değişimlerin GDM'si olan ve olmayan hastalarda karşılaştırılması

Gereçler ve yöntem: GDM için 24-28. gebelik haftalarında taranan ve ilk iki trimesterde de hemogram testi yapılmış olan gebeler retrospektif olarak araştırıldı. Trombosit kütle endeksi (TKE), nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranı (TLO) hesaplandı. İleride GDM gelişen ve gelişmeyen hastaların ilk trimester hematolojik endeksleri ve bu endekslerin progressif değişimleri karşılaştırıldı.

Sonuç: Üç yüz atmış sekiz hasta çalışmaya dahil edildi ve GDM %17,9 oranında saptandı. İlk trimester endeksleri arasında TLO haricinde fark tespit edilmedi. TLO GDM'li hastalarda daha düşük idi fakat bağımsız bir prediktör olarak bulunmadı. Normal glisemik gebelerde hemoglobin, hematokrit, lenfosit, trombosit, ortalama trombosit hacmi (MPV), plateletkrit (PCT), trombosit büyük hücre oranı (PLCR) ve TKE değerlerinde ilk trimestere oranla ikinci trimesterde anlamlı düşüş olduğu görüldü. Beyaz küre (WBC), nötrofiller, çekirdekli kırmızı kan hücreleri (NRBC), immatür granülositler ve NLO anlamlı olarak yükselirken, kırmızı hücre dağılım genişliği (RDW), trombosit dağılım genişliği (PDW) ve TLO'da anlamlı değişim gözlenmedi. GDM'li hastalarda ise hemoglobin, hematokrit, lenfosit, trombosit ve TKE'de belirgin düşüş görülürken, WBC, nötrofiller, MPV, immatür granülositler ve NLO birinci trimestere göre yükselmişti. RDW, PDW, PCT, PLCR, NRBC ve TLO'da değişim gözlenmedi.

Sonuç: İlk trimesterdeki hiçbir hematolojik endeks, gelişecek GDM'yi öngörme yetisine sahip değildir. MPV'de gözlenen progresif değişimler GDM gelişmesinin değerlendirilmesi için bir indikatör olarak kullanılabilir.

Anahtar Kelimeler: Hematolojik endeksler, gestasyonel diyabetes mellitus, ortalama trombosit hacmi, inflamatuvar belirteçler, tam kan sayımındaki değişimler

ABSTRACT

Aim: To assess the predictive role of hematological indices in the first trimester of pregnancy for gestational diabetes mellitus (GDM) and to compare the progressive changes in these indices between patients with and without GDM in their first and second trimesters.

Materials and Methods: Pregnant women screened for GDM in 24-28 gestational weeks and who had CBC test in the first and second trimesters were retrospectively investigated. Platelet mass index (PMI), neutrophil-to-lymphocyte ratios (NLR) and platelet-to-lymphocyte ratios (PLR) were calculated. The first trimester hematological indices were compared between normal glycemic patients and the patients with subsequent GDM. The progressive changes of these indices were compared.

Results: Three-hundred-sixty-eight women were enrolled and 17.9% had GDM. There was no difference between first trimester hematological indices, except PLR which was lower in GDM group, however, PLR was not an independent predictor. In normal-glycemic pregnant women hemoglobin, hematocrit, lymphocytes, platelets, mean-platelet-volume (MPV), plateletcrit (PCT), platelet-large-cell-ratio (PLCR) and PMI decreased significantly from first trimester to second trimester. White-blood-cells(WBC), neutrophils, nucleated-red-blood-cells(NRBC), immature granulocytes and NLR increased significantly, while no significant changes were detected in red-cell-distribution-width(RDW), platelet-distribution-width(PDW) and PLR. In GDM patients, hemoglobin, hematocrit, lymphocytes, platelets and PMI significantly decreased while WBC, neutrophils, MPV, immature granulocytes and NLR increased from first trimester to second trimester. RDW, PDW, PCT, PLCR, NRBC and PLR did not change.

Conclusion: None of the first trimester hematological indices have a predictive ability for subsequent GDM. The progressive changes in MPV can be used as an indicator to assess the development of GDM.

Key Words: Hematological indices; gestational diabetes mellitus; mean platelet volume; inflammatory markers; change in complete blood count parameters

Sorumlu Yazar/ Corresponding Author:
Pelin AYTAN
Mersin University Faculty of Medicine, Department of Hematology
E-mail: drpelinaytan@gmail.com

Başvuru tarihi : 06.10.2020
Kabul tarihi : 12.10.2020

INTRODUCTION

Gestational diabetes mellitus (GDM) which is defined as carbohydrate intolerance that develops during pregnancy, is considered to be the most common metabolic disorder seen in pregnancy and yet has an increasing trend (1). It develops when pancreas cannot compensate increased insulin demand that resulted from the peak in the secretion of placental hormones. Chronic subclinical inflammation with insulin resistance are considered to be the main underlying mechanisms (2).

Chronic subclinical inflammation is the state of increased proinflammatory and acute phase proteins with increased immune cells (3, 4). Some of the indices of complete blood count (CBC) including, white blood cells (WBC), red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT) and blood cell subtype ratios as platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR) and platelet mass index (PMI) have been proposed as markers of systemic inflammation (5). Recently these markers are suggested to differ in GDM patients in different studies (6-9). However, in some other studies no significant differences were observed in these markers between patients with and without GDM (10-15).

The pathophysiological process of GDM occurs months before the diagnosis and markers related to the disease may be present in the blood before the clinical diagnosis is made (16). Therefore, in light of the contrary findings, the aim of the present study was to assess the predictive role of hematological indices that are parts of a simple CBC test performed in the first trimester of pregnancy for development of GDM and to compare the progressive changes in these indices between patients with and without GDM throughout the first and the second trimesters.

MATERIAL AND METHOD

All the pregnant women who were screened for GDM in their 24-28 gestational weeks with a 75 g oral glucose tolerance test (OGTT) and to whom a CBC was ordered in the first trimester and again in the second trimester during GDM screening in obstetrics department of our clinic between January 2017 and January 2020 were included in this retrospective cohort study. Data were obtained from the electronic data base of the hospital. Screening is offered to all pregnant women in our clinic between 24-28 gestational weeks unless she has risk factors for earlier testing (1). Patients with a known systemic disease including rheumatologic disorders, thyroid abnormalities, hypertension, preeclampsia, renal failure, cardiac diseases, any kind of autoimmune diseases, malignancies and respiratory diseases were excluded. Women who were using aspirin or heparin and steroids for any reason were also excluded. The institutional ethics approval was obtained for the study (2020/473).

The CBC was analyzed with the SYSMEX-XN-1000/23797 hemogram device. The assessed parameters in CBC were hemoglobin, hematocrit, red blood cells, mean corpuscular volume (MCV), MCH concentration, WBC (including neutrophils, lymphocytes and their percentages), platelets, PDW, MPV, RDW, nucleated red blood cell (NRBC), NRBC percentage, PCT, platelet large cell ratio (P-LCR), immature granulocytes (IG) and IG percentage. Platelet mass index (PMI) was calculated by multiplying platelet number with MPV and divide the result by 1000. NLR and PLR are calculated by dividing the absolute neutrophil and platelet counts by the absolute lymphocyte count.

The screening for GDM using a 75-g, 2-hour OGTT had been performed in the morning after an 8 to 14 hours fast. A fasting blood sample was obtained for CBC and OGGT. Then the patient was instructed to drink a standard liquid containing 75 g glucose. The blood sample was obtained again two times every 60 minutes. She was not allowed to eat or drink during the test. GDM was diagnosed when any single threshold value was met or exceeded fasting value, 92 mg/dL; 1-hour value, 180 mg/dL; or 2-hour value, 153 mg/dL (17).

Statistical analysis was accomplished with statistical program for social sciences (SPSS 22, demo version, IBM). Normality of the data was tested with Kolmogorov-Smirnov Test. Normally distributed data were expressed as mean ± standard deviation and compared with independent and paired samples t tests where appropriate. Mann-Whitney U and Wilcoxon signed-rank tests (where appropriate) were used for comparison of non-normally distributed data which were expressed as median (interquartile range). Binomial data were expressed as percentages and compared with chi square test. Correlation analysis (Pearson or Spearman coefficients where appropriate) was done to find factors that had correlations with diagnosis of GDM and a regression analysis was performed with these factors that were found to have significant correlation in order to find out the independent predictors of GDM diagnosis. A value of ≤0.05 was considered as significant.

RESULTS

A total of 1177 pregnant women had been screened for GDM in 24-28 gestational weeks between January 2017 – January 2020 in our clinic and 368 women fulfilled the inclusion criteria. There were 66 patients (17.9%) who were diagnosed to have GDM. GDM patients were significantly older and had experienced more pregnancies (32.8 ± 4.6 vs 29.7 ± 4.8 years, p: <0.01; 2.6 ± 1.4 vs 2.2 ± 1.5, p:0.008, respectively). Groups were similar with respect to delivery week, fetal birth weight, umbilical blood pH, 1 and 5th minute APGAR scores; however, more newborns of GDM mothers had been admitted to the newborn intensive care unit for any reason (30.8% vs 13.6%, p:0.009).

The comparison of first trimester CBC parameters and the PLR, NLR and PMI values in the groups were depicted in table 1.

Table 1. Comparison of the first trimester complete blood count parameters of the patients with and without gestational diabetes (shown as mean ± standard deviation or median (interquartile range) where appropriate)

	Controls	GDM patients	p
Hemoglobin (g/dL)	11.9 ± 1.3	12.1 ± 1.2	0.567
Hematocrit (%)	35.5 ± 2.9	35.8 ± 3.5	0.630
RDW	13.8 ± 1.8	13.6 ± 1.6	0.347
White Blood Cells	9.5 ± 2.6	9.7 ± 2.4	0.602
Neutrophils	6.6 ± 2.3	6.7 ± 1.9	0.717
Lymphocytes	2.1 ± 0.6	2.2 ± 0.6	0.218
Monocytes	0.58 (0.24)	0.63 (0.24)	0.204
Basophils	0.04 (0.02)	0.03 (0.04)	0.928
Eosinophils	0.1 (0.11)	0.11 (0.16)	0.659
Platelets(/mm^3)	263,914 ± 74370	254,510 ± 48,807	0.400
Platelet Distribution Width	12.7 ± 2.3	12.9 ± 1.9	0.569
Mean Platelet Volume	10.7 ± 0.9	10.8 ± 0.9	0.510
PCT	0.28 (0.07)	0.27 (0.08)	0.421
PLCR	30.4 ± 8	30.4 ± 7.2	0.692
NRBC	0 (0)	0 (0.1)	0.221
Immature granulocytes	0.04 (0.03)	0.04 (0.04)	0.785
PLR	133.2 ± 46.6	122.2 ± 40	0.03
NLR	3.4 ± 1.8	3.2 ± 1.3	0.516
PMI	2794.5 ± 720	2715.8 ± 448	0.470

RDW: Red cell distribution width, PCT: Plateletcrit, PLCR: Platelet large cell ratio, NRBC: Nucleated red blood cell, PLR: platelet-to- lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, PMI: Platelet mass index

Except PLR, which was lower in the GDM patients, groups were similar with respect to hematologic indices. In the control group NRBC was positive in 9.5% in the first trimester and 15.1% in the second trimester. In GDM patients NRBC was positive in 15.1% and 30.5% in the first and second trimesters respectively.

The progressive changes of the CBC parameters and the comparison of these changes in the groups were shown in table 2.

In healthy pregnant women without GDM hemoglobin, hematocrit, lymphocytes, platelets, MPV, PCT, PLCR and PMI were found to decrease significantly from first trimester to second trimester (Table 2). WBC, neutrophils, NRBC, immature granulocytes and NLR had a tendency to increase significantly, while no significant changes were detected in RDW, PDW and PLR. In pregnant women with GDM hemoglobin, hematocrit, lymphocytes, platelets and PMI significantly decreased while WBC, neutrophils, MPV, immature granulocytes and NLR increased from first trimester to second trimester. RDW, PDW, PCT, PLCR, NRBC and PLR did not change (Table 2).

There was no statistically significant difference between the amount of increases or decreases in the groups (Table 2). The progressive changes seen in MPV was contrary in the patients with and without GDM, it increased significantly in GDM patients, but decreased in the control patients (Table 2).

Table 2. Comparison of the first trimester complete blood count parameters of the patients with and without gestational diabetes (shown as mean ± standard deviation or median (interquartile range) where appropriate)

	Controls			GDM patients			Change*
	First trimester	Second Trimester	p	First Trimester	Second Trimester	p	p
Hemoglobin (g/dL)	11.9 ± 1.3	11.4 ± 1	<0.01	12.1 ± 1.2	11.3 ± 1.1	<0.01	0.756
Hematocrit (%)	35.5 ± 2.9	33.6 ± 2.7	<0.01	35.8 ± 3.5	33.6 ± 2.9	<0.01	0.674
RDW	13.8 ± 1.8	13.9 ± 1.4	0.36	13.6 ± 1.6	13.8 ± 1.3	0.301	-
White Blood Cells	9.5 ± 2.6	10.3 ± 2.4	<0.01	9.7 ± 2.4	10.4 ± 2.4	<0.01	0.053
Neutrophils	6.6 ± 2.3	7.6 ± 2.2	<0.01	6.7 ± 1.9	7.5 ± 1.9	0.038	0.120
Lymphocytes	2.1 ± 0.6	1.9 ± 0.6	<0.01	2.2 ± 0.6	1.96 ± 0.5	<0.01	0.258
Monocytes	0.58 (0.24)	0.61 (0.25)	0.033	0.63 (0.24)	0.69 (0.24)	0.165	-
Basophils	0.04 (0.02)	0.04 (0.02)	0.565	0.03 (0.04)	0.03 (0.03)	0.190	-
Eosinophils	0.1 (0.11)	0.1 (0.13)	0.053	0.11 (0.16)	0.12 (0.11)	0.179	-
Platelets(/mm^3)	263,914 ±74370	238,443 ±6334	<0.01	254,510 ±48,807	235,666 ±55,340	0.005	0.337
PDW	12.7 ± 2.3	12.5 ± 2.1	0.39	12.9 ± 1.9	13.1 ± 2	0.148	-
Mean platelet volume	10.7 ± 0.9	10.6 ± 0.9	0.07	10.8 ± 0.9	10.9 ± 0.9	0.02	-
PCT	0.28 (0.07)	0.25 (0.07)	<0.01	0.27 (0.08)	0.26 (0.06)	0.168	-
PLCR	30.4 ± 8	29.6 ± 7.9	0.03	30.4 ± 7	31.1 ± 8.9	0.07	-
NRBC	0 (0)	0 (0)	0.01	0 (0.1)	0 (0.1)	0.157	-
Immature granulocytes	0.04 (0.03)	0.09 (0.1)	<0.01	0.04 (0.04)	0.08 (0.09)	<0.01	0.258
PLR	133.2 ±46.6	133.4 ±49.2	0.95	122.2 ±40	128.3 ±46.5	0.142	-
NLR	3.4 ± 1.8	4.2 ± 1.9	<0.01	3.2 ± 1.3	3.9 ± 1.1	<0.01	0.671
PMI	2794.5 ± 720	2511.9 ± 600	<0.01	2715.8 ± 448	2529.6 ± 496	0.017	0.104

*. Comparison of the amount of change in the parameters that had a significant change from first to second trimester.

RDW: Red cell distribution width, PDW: Platelet distribution width, PCT: Plateletcrit, PLCR: Platelet large cell ratio, NRBC: Nucleated red blood cell, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, PMI: Platelet mass index

Among first trimester hematologic indices, only PLR was found to be correlated with subsequent GDM (Table 3); however, this significance had disappeared in regression analysis indicating that only maternal age was an independent predictor of GDM (Table 4).

Table 3. Correlation analysis of possible factors related with gestational diabetes.

	Correlation Coefficient	p
Age (years)	0.230	<0.0001
Gravidity	0.140	0.007
PLR-	0.126	0.029

PLR: Platelet to lymphocyte ratio

Table 4. Regression analysis of factors independently associated with gestational diabetes.

	β	t	p	95% Confidence Interval
Age	0.228	3,365	0.001	0.008 - 0.03
Gravidity	-0.022	-0.323	0.747	-0.043 - 0.031
PLR	-0.093	-1.513	0.32	-0.002 - 0

PLR: Platelet to lymphocyte ratio

DISCUSSION

In the present study it was found that none of the parameters in a CBC test in the first trimester have a predictive role for subsequent GDM. Progressive changes in CBC parameters are similar in healthy and patients who will develop GDM in the second trimester except MPV, which tends to increase in subsequent GDM patients, contrary to the health pregnant women without GDM.

Many physiological changes in hematological profile occur during pregnancy which may appear to be pathological in the non-pregnant. The renin-angiotensin- aldosterone system is activated which results in 40-45% increase in plasma volume (18). Erythropoietin increases throughout pregnancy and as a result red blood cell mass increases by 15-20%. This relatively small increase in red blood cell mass compared to plasma volume leads to a fall in hemoglobin concentration by 1-2 g/dL by the late second trimester which is termed as the physiological anemia of pregnancy (19). RDW is a marker for anisocytosis and there is conflicting data with regard to its progression in pregnancy. Some authors reported a temporal increase in RDW; however, there are studies that did not find significant changes throughout the pregnancy (20, 21). WBC count increases due to the physiologic stress induced by pregnancy and neutrophils contribute most of the overall higher WBC count (22). Immature forms, myelocytes and metamyelocytes, may be detected in healthy pregnant women without reflecting a pathologic state (22).

Lymphocyte count decreases through first and second trimester (22). Monocytes increase in the first trimester and then decrease (23). There is no significant change in eosinophil and basophil counts (24). Platelet count decreases because of hemodilution, increased platelet activation and consumption, particularly in the third trimester (25). PDW increases continuously as pregnancy progresses and there is little change in MPV (22, 26). The aim was to compare the progressive changes in hematological indices throughout the first two trimesters in healthy pregnant women and pregnant women who would develop subsequent GDM. The progressive changes that occur in the healthy pregnant women are in accordance with the literature. In addition, we showed an increase in the amount of nucleated red blood cells as the pregnancy advances. There are some significant differences in the pattern of changes in the GDM group. The main difference is in the progression of MPV which has a tendency to decrease in healthy pregnant women, but increases significantly in GDM patients. In addition, PLCR and PCT decrease significantly in the healthy group. In the GDM patients although not significant, PLCR and PDW have a tendency to increase and PCT has a tendency to decrease. In addition, the monocytes in the healthy group increases significantly in the second trimester in the healthy group; however, such a significant increase does not occur in the GDM group.

It is known that platelet activity is correlated with changes in platelet volume, the larger being more active (27). MPV, PDW and PLCR are indices that represent platelet activity. Especially MPV can be used as an indicator of platelet activation (28). MPV has been reported to be increased in GDM patients and it has been suggested as a predictive marker for GDM (8, 29). Some authors suggested that the positive relationship between an increased glucose level and increased MPV is a unique phenomenon of diabetes (30). Although MPV was higher in the GDM patients, first trimester MPV values did not differ significantly between the groups. However, during the course of pregnancy MPV significantly increased in the patients who would develop GDM. The same progressive changes are true for PDW and PLCR which tend to increase in the GDM patients; however, the increase of MPV is prominent. This study is valuable as it compares the progressive changes in the hematological indices including MPV before the GDM occurs. From this point we conclude that changes in MPV can be used as an indicator to assess the development of GDM. Monitorization of the other platelet indices including PDW and PLCR may also be valuable.

Chronic low-grade inflammation is considered to be one of the key components of the pathogenesis in GDM (31, 32). This inflammation triggers subsequent changes in hematological parameters including platelets, white blood cells and red blood cells. Platelet activation that alters the platelet indices including MPV, PDW and PCT (7, 33) and indices such as PLR and NLR have been shown to be affected in GDM patients (5, 7, 8, 11, 34), although there are studies that reported no significant changes (11-15). Similarly, there are contradictory results with respect to WBC and red blood cells (9, 14). We had shown that in the second trimester of pregnancy RDW and NRBC are independently associated with GDM (10). However, in the present study such an association could not be found in the first trimester. It has been shown that chronic inflammation may cause RDW level elevation and elevated RDW may reflect a status of high inflammation and oxidative stress (35) and high RDW was associated with high risk of developing diabetes (36). GDM develops when the pancreatic insufficiency becomes obvious as the placental hormones increase progressively from first to second trimester. It is true that the pathophysiological process of GDM occurs weeks before the diagnosis. From this point it seems that the inflammation progresses within gestational weeks and the hematologic indices are not yet affected in the first trimester.

Recently NLR, PLR and PMI have gained scientific interest because of their ability to reflect systemic inflammation (35) and the roles of NLR, PLR and PMI in prediction of GDM were assessed (5, 10, 11). Yilmaz et al (5) reported that NLR was significantly higher in GDM patients compared with normal glycemic pregnant women and was a powerful predictor of GDM, while Sargin et al (11) reported no predictive ability of NLR. PMI has been suggested to be a better parameter of inflammation than MPV (37). We had shown that second trimester PMI had no predictive ability for GDM (10). In a recent study Sun et al found that first trimester values of neutrophils, WBC and NLR were all associated with the development of GDM, but that neutrophil count had the highest OR (6). In the present study first trimester neutrophils, NLR and PMI were found to be similar in the groups. Only first trimester PLR was found to be significantly lower in the patients who would develop subsequent GDM and negatively correlated with development GDM; however, the significance disappeared in the regression analysis indicating that first trimester PLR is not an independent predictor of GDM. None of these systemic inflammatory response markers seem to have a predictive role for GDM in the first trimester.

The main strength of this study is that the progressive changes in the hematological indices of the normal glycemic pregnant women and women who would develop subsequent GDM are presented and compared. This comparison is presented for the first time in Turkish pregnant women as far as we are concerned. All the patients are from the same clinic and followed-up with the same protocols. The blood samples had been analyzed with the same device. The main limitation of studies like ours is that that the results of the blood samples are laboratory and analyzer dependent and may be unique to the studied population. The results may be highly variable. These should be kept in mind while interpreting the presented data. Retrospective design was another limitation. Therefore, prospective, multicenter studies that use the same analyzers in different populations with larger sample sizes would be more informative.

In conclusion none of the first trimester hematological indices have a predictive ability for development of subsequent GDM. The progressive changes in some hematological indices that occur in pregnant women who would develop GDM differ from that of normal glycemic pregnant women. Changes in MPV can be used as an indicator to assess the development of GDM and monitorization of the other platelet indices including PDW and PLCR may also be valuable.

REFERENCES

1. ACOG Practice Bulletin No. 190 Summary: Gestational Diabetes Mellitus. Obstet Gynecol 2018:131(2):406-8.

2. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286(3):327- 34

3. Fowler AJ, Agha RA. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography-the growing versatility of NLR. Atherosclerosis 2013;228(1):44-5.

4. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Haematol 2013;88(1):218-30.

5. Yılmaz Z, Yılmaz E, İçer B, Küçüközkan T. Association of complete blood count parameters with gestational diabetes mellitus. Gynecology Obstetrics & Reproductive Medicine 2017;23(2):65-9.

6. Sun T, Meng F, Zhao H, Yang M, Zhang R, Yu Z, et al. Elevated first-trimester neutrophil count is closely associated with the development of maternal gestational diabetes mellitus and adverse pregnancy outcomes. Diabetes

2020;69(7):1401-10

7. 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.

8. Zhou Z, Chen H, Sun M, Ju H. Mean platelet volume and gestational diabetes mellitus: a systematic review and meta-analysis. J Diabetes Res 2018;2018:1985026.

9. Yang H, Zhu C, Ma Q, Long Y, Cheng Z. Variations of blood cells in prediction of gestational diabetes mellitus. J Perinat Med 2015;43:89–93.

10. Aytan P, Bozkurt Babuş S, Sakarya Ö, Sakarya Ö, Çi□ftçi□ R, Aytan H. Can a simple complete blood count predict gestational diabetes mellitus?. J Contemp Med. 2020;10(3):336-41.

11. Sargin MA, Yassa M, Taymur BD, Celek 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 2016:657-66.

12. Chen X, Fang L, Lin H, Shen P, Zhang T, Li H, et al. The relationship between type 2 diabetes and platelet indicators. Iran J Public Health 2017;46:1211–6.

13. 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;44:121–5.

14. Mertoglu C, Gunay M, Gungor M, Kulhan M, Kulhan NG. A study of inflammatory markers in gestational diabetes mellitus. Gynecology Obstetrics & Reproductive Medicine 2019;25(1):7-11

15. Gorar S, Abanonu GB, Uysal A, Erol O, Unal A, Uyar S, et al. Comparison of thyroid function tests and blood count in pregnant women with versus without gestational diabetes mellitus. J Obstet Gynaecol Res 2017;43:848–54.

16. Beneventi F, Simonetta M, Lovati E, Albonico G, Tinelli C, Locatelli E, et al. First trimester pregnancy-associated plasma protein-A in pregnancies complicated by subsequent gestational diabetes. Prenat Diagn. 2011;31(6):523-8

17. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. International association of diabetes and pregnancy study groups consensus panel. Diabetes Care 2010;33:676–82.

18. Carlin A, Zarko A. Physiological changes of pregnancy and monitoring. Best Pract Res Clin Obstet Gynaecol. 2008;22(5):801–23.

19. Heidemann BH, McClure JH. Changes in maternal physiology during pregnancy. Br J Anaesth. 2003;3(3):65–8.

20. Li A, Yang S, Zhang J, Qiao R. Establishment of reference intervals for complete blood count parameters during normal pregnancy in Beijing. J Clin Lab Anal. 2017;31(6):e22150.

21. Amah-Tariah FS, Ojeka SO, Dapper DV. Haematological values in pregnant women in Port Harcourt, Nigeria II: Serum iron and transferrin, total and unsaturated iron binding capacity and some red cell and platelet indices. Niger J Physiol Sci. 2011;26(2):173-8.

22. Chandra S, Tripathi AK, Mishra S, Amzaru M, Vaish AK. Physiological changes in hematological parameters during pregnancy. Indian J Hematol Blood Transfus. 2012;28(3):144–6.

23. Kline AJ, Williams GW, Hernandez-Nino J. D-Dimer concentration in normal pregnancy: new diagnostic thresholds are needed. Clin Chem. 2005;51(5):825–9.

24. Edlestam G, Lowbeer C, Kral G, Gustafsson SA, Venge P. New reference values for routine blood samples and human neutrophilic lipocalin during third trimester pregnancy. Scand J Clin Lab Inv. 2001;61:583–92.

25. Shehlata N, Burrows RF, Kelton JG. Gestational thrombocytopenia. Clin Obstet Gynecol. 1999;42:327–34.

26. Ahmed Y, van Iddekinge B, Paul C, Sullivan MHF, Elder MG. Retrospective analysis of platelet numbers and volumes in normal pregnancy and pre-eclampsia. Br J Obstet Gynaecol. 1993;100:216–20.

27. Ranjith MP, Divya R, Mehta VK, Krishnan MG, Raj RK, Kavishwar A. Significance of platelet volume indices and platelet count in ischaemic heart disease. J Clin Pathol, 2009;62:830–33.

28. Jagroop IA, Tsiara S, Mikhailidis DP. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets. 2003;14(5):335-6.

29. Yang H, Zhu C, Ma Q, Long Y, Cheng Z. Variations of blood cells in prediction of gestational diabetes mellitus. J Perinat Med. 2015;43(1):89-93.

30. 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;35:1074-8.

31. Lekva T, Norwitz ER, Aukrust P, Ueland T. Impact of systemic inflammation on the progression of gestational diabetes mellitus. Curr Diab Rep 2016;16(4):26.

32. Hernandez TL, Van Pelt RE, Anderson MA, Reece MS, Reynolds RM, de la Houssaye BA, et al. Women with gestational diabetes mellitus randomized to a higher-complex carbohydrate/low-fat diet manifest lower adipose tissue insulin resistance, inflammation, glucose, and free fatty acids: a pilot study. Diabetes Care 2016;39(1):39-42.

33. Kim JH, Bae HY, Kim SY. Response: clinical marker of platelet hyperreactivity in diabetes mellitus. Diabetes Metab J 2013;37:423-8.

34. Sefil F, Ulutas KT, Dokuyucu R, Sumbul AT, Yengil E, Yagiz AE, et al. Investigation of neutrophil lymphocyte ratio and blood glucose regulation in patients with type 2 diabetes mellitus. J Int Med Res 2014;42(2):581-8.

35. 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;28(3):030502.

36. Wang J, Zhang Y, Wan Y, Fan Z, Xu R. The relationship between red blood cell distribution width and ıncident diabetes in chinese adults: a cohort study. J Diabetes Res 2020;2020:1623247.

37. Okur N, Buyuktiryaki M, Uras N, Oncel MY, Ertekin O, Canpolat FE, et al. Platelet mass index in very preterm infants: can it be used as a parameter for neonatal morbidities? J Matern Fetal Neonatal Med 2016;29:3218-22.