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Can neutrophil-lymphocyte and platelet-lymphocyte ratios predict threatened abortion and early pregnancy loss?

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ABSTRACT

Objectives: An investigation of the importance of hematological inflammatory markers on the prognosis of first trimester pregnancies and their role in predicting threatened abortion and early pregnancy loss.

Material and methods: This study was carried out in the Obstetrics and Gynecology Department of the Faculty of Medicine in our University between January 2018 and May 2019. Three-hundred individuals, 100 of them diagnosed with early pregnancy loss (EPL), 100 diagnosed with threatened abortion (TA) and 100 healthy control patients (HC), participated in the study.

Results: There were no statistically significant differences in terms of hemoglobin, platelet, neutrophil count and NLR between the three groups. The RBC counts were significantly lower in EPL and TA compared to HC. Similarly, it was determined that the MPV value was significantly lower in EPL compared to HC. On the other hand, there was no difference in MPV between TA and HC. The PLR was higher in EPL and TA.

Conclusions: MPV, RBCs and PLR values were strongly associated with first-trimester miscarriage. These economical and easily measurable platelet indices can be used to predict fetal losses.

Key words: complete blood count; first-trimester abortion; inflammation; neutrophils; platelet count; risk factors

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INTRODUCTION

Early pregnancy loss is commonly seen, and its incidence has been reported to be in the range of 50 to 70% in all conceptions [1]. The exact reason for early pregnancy loss has not been fully revealed. Although causal relationships and mechanisms cannot be fully explained, chromosomal anomalies are held responsible for nearly half of the cases [2, 3], while the other half remain unknown. In recent years, data have indicated that a significant proportion of abortions have emerged as a result of problems with immunological mechanisms and endocrinological factors that both mirror and are part of the immunological and haematological structure [4, 5].

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte (PLR) ratios are markers showing inflammatory status. These rates could be easily determined with the blood test. These values chiefly indicate the presence of inflammatory load and are therefore utilized as prognostic indicators in many branches of medicine, and they have been frequently reported on and tested [6]. When the literature is examined, NLR and PLR have been examined in previous studies for pathological conditions such as gynecological cancers [7], ovarian hyperstimulation syndrome [8], early ovarian failure [9], endometriosis [10], hyperemesis gravidarum [11], gestational diabetes [12], preeclampsia [13], pregnancy-associated intrahepatic cholestasis [14] and other diseases. The increased values of these parameters must be taken into serious consideration, especially during pregnancy. Numerous physiological changes occur during pregnancy, and these changes lead to special reference values for the evaluation of laboratory assays.

This research aimed to determine pregnancy-related reference values for NLR and PLR in accordance with the first trimester and investigated the importance of hematological inflammatory markers on the prognosis of first trimester pregnancies.

MATERIAL AND METHODS

Study design and patient population

The present study adopted a retrospective, one-centre, case-control approach and was carried out in the Obstetrics

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and Gynecology Department of our University. The research was carried out in compliance with the approved guidelines and the principles expressed by the Helsinki Declaration [Ethics Committee Date and Number: (09.04.2019-03/09)].

A total of 300 patients were included this study. One hundred of them were the threatened abortion group (TAG), one hundred of them were the early pregnancy loss group (EPLG) and 100 of them were the healthy control group (HCG). The patient data were collected from hospital records over the last 2 years. Demographic parameters were recorded from patient files and laboratory parameters were recorded from complete blood cell count (CBC) results at the first trimester.

The first-trimester (7–14 weeks) CBC values were determined for all patients. Patients in any condition that could affect blood parameters such as multiple pregnancy, fetal infections, and amniocentesis were excluded from the study.

In the case of the presence of multiple CBC results, the result during 7 weeks of pregnancy was taken into consideration and used in the statistical evaluation. NLR was calculated by dividing the number of neutrophils by the number of lymphocytes, and PLT by dividing the number of platelets by the number of lymphocytes. NLR, PLR, mean platelet volume (MPV), neutrophil counts, platelet counts, lymphocyte counts, red blood cell (RBC) counts and hemoglobin levels were determined for the three study groups. In all cases, blood samples were collected in tripotassium Ethylenediaminetetraacetic acid (EDTA) tubes. All measurements of hematologic parameters were performed using a Beckman Coulter blood count analyzer (Beckman Coulter Inc., CA, USA) 30 minutes after blood collection.

Statistical Analyses

The statistics software package SPSS 25 (IBM, Armonk, NY: IBM Corp.) was used for the statistical evaluations in the present study. Descriptive statistics (mean, standard deviation, median, minimum value, maximum value and percentage value) were determined for discrete and continuous variables. Also, Levene's test was adopted for the determination of the homogeneity of the variance results. The normality of the data's distribution was evaluated using the Shapiro–Wilk test. The differences between three or more groups is determined by a one-way ANOVA test when the parametric test prerequisites are fulfilled, and the Kruskal Wallis test is used when such prerequisites are not fulfilled. A multiple comparison test, the Bonferroni correction method, is used to evaluate the significant results of three or more groups. The determined variable cut-off values for RBCs (10^6 uL), hemoglobin (g/dL), platelets (10^3 uL), MPV (fL, mean ± SD), neutrophils (10^3 uL), lymphocytes (10^3 uL), NLR and PLR responses were evaluated by receiver operating characteristic (ROC) analysis. Also, the Area Under the Curve (AUC) value, sensitivity and specificity values were calculated. The level of significance was set as $p < 0.05$.

RESULTS

The results obtained in the present study revealed that the differences in age, gravidity, parity, height, body weight, BMI, smoking habits and alcohol intake values were statistically not significant between the pregnant women, the women with a history of early pregnancy loss (EPL) and threatened abortion (TA), and the healthy group ($p > 0.05$ for each).

The differences in hemoglobin count, platelet count, neutrophil count and NLR values between the three groups were not statistically significant ($p = 0.15$, $p = 0.45$, $p = 0.65$ and $p = 0.19$, respectively) (Tab. 1).

The RBC counts were significantly lower in EPLG and TAG compared to HCG (4.63 ± 0.32 vs 4.8 ± 0.35 10^6 uL and 4.52 ± 0.39 vs 4.8 ± 0.35 10^6 uL for $p < 0.001$, respectively). Similarly, MPV was found to be significantly lower in EPLG compared to HCG (8.71 ± 0.93 fL vs 10.6 ± 0.85 fL for $p < 0.001$, respectively). On the other hand, there was no difference in MPV between TAG and HCG (10.01 ± 1.25 fL vs 10.6 ± 0.85 fL for $p > 0.05$). The PLR was higher in EPLG and TAG (148.01 ± 38.24 vs 122.9 ± 29.65 and 134.26 ± 42.51 vs 122.9 ± 29.65 for $p < 0.001$, respectively) (Tab. 1).

Prognostic values of the optimum cut-offs for first-trimester neutrophil counts, lymphocyte counts, platelet counts, mean platelet volume, neutrophil–lymphocytes ratio and platelet–lymphocyte ratio for predicting EPL and TA are summarized in Tables 2a and 2b.

A cut-off value of ≤ 9.6 in the ROC analysis — performed to investigate the effect of the MPV value in predicting EPL — produced a sensitivity of 88% and a specificity of 88%. The Area Under the Curve (AUC) for the MPV was 0.937 (95% CI: 75.7 to 95.5 %, $p < 0.001$) (Fig. 1a).

The AUC for PLR was 0.686 ($p < 0.001$) in EPLG (Fig. 1b). The sensitivity and specificity of the PLR were determined to be 78% and 50%, respectively, at a threshold PLR value of > 115.41. Values > 115.41 were significantly related to an increased risk of EPL.

The AUC for RBCs was found to be 0.633 ($p < 0.017$) in EPLG (Fig. 1c). The sensitivity and specificity of the RBCs were determined to be 46% and 76%, respectively, at a threshold RBC value of ≤ 4.57 for EPL.

A cut-off value of ≤ 9.7 in the ROC analysis — performed to investigate the effect of the MPV value in predicting TA — produced a sensitivity of 40% and specificity of 84%. The AUC for the MPV was 0.631 ($p < 0.019$) (Fig. 2a).

The AUC for RBCs was found to be 0.698 ($p < 0.01$) (Fig. 2b). The sensitivity and specificity of the RBCs were found to be 54% and 84%, respectively, at a threshold RBC value of ≤ 4.45 in TA.

Table 1. Can neutrophils count lymphocytes count platelet count mean platelet volüme neutrophils-lymphocytes ratio and platelets-lymphocytes ratio during the first trimester of pregnancy predict early pregnancy loss and threatened abortion?

Demographic and clinical characteristics of patients	Early pregnancy loss	Threatened abortion	Healty control	p
Age [years]	27.7 ± 4.7	28.1 ± 4.0	27.1 ± 5.2	0.56
Gravida [number]	2.2 ± 2.7	2.8 ± 1.8	2.6 ± 1.8	0.11
Parity [number]	2.0 ± 1.1	1.9 ± 1.1	2.2 ± 3.7	0.84
Gestational age [week]	10 ± 2.1	11 ± 0.9	10 ± 1.8	0.91
RBCs [10^6 uL]	4.63 ± 0.32[a]	4.52 ± 0.39[a]	4.8 ± 0.35[b]	0.001**
Hemoglobin [g/dL]	12.63 ± 1.57	12.86 ± 1.13	13.15 ± 1.17	0.15
Platelets [10^3 uL]	271.62 ± 68.65	259.22 ± 45.89	272.64 ± 60.77	0.45
MPV [fL. mean ± SD]	8.71 ± 0.93[a]	10.01 ± 1.25[b]	10.6 ± 0.85[b]	0.001**
Neutrophils [10^3 uL]	5.81 ± 2.18	6.16 ± 2.12	6.11 ± 1.74	0.65
Lymphocytes [10^3 uL]	1.91 ± 0.57[a]	2.06 ± 0.51[b]	2.29 ± 0.57[c]	0.001**
NLR	3.19 ± 1.32	3.22 ± 1.75	2.77 ± 0.94	0.19
PLR	148.01 ± 38.24[a]	134.26 ± 42.51[b]	122.9 ± 29.65[c]	0.001**

RBCs — red blood cells; NLR — neutrophils-lymphocytes ratio; PLR — platelets-lymphocytes ratio; MPV — mean platelet volüme; **p < 0.01

DISCUSSION

Sacks et al. [15] reported that there was a large proinflammatory macrophage and natural killer cell flow in human decidua in the first trimester detected in the fourth week of pregnancy. In the present case-control study, the hypothesis was structured on the possible association of NLR and PLR — two of the systemic inflammatory markers in the first trimester of pregnancy — with successful pregnancy results in the first trimester. Based on the literature research carried on this subject, this is the first case-control study to examine the efficacy of hematological inflammatory markers for diagnosing EPL and TA.

Early pregnancy is a hypoxic case that may quicken angiogenesis. Moreover, in a recent study, it has been reported that severe hypoxia and abnormal vascular endothelial growth factor signals may cause pregnancy loss [16]. All the markers studied are expensive and involve non-routine tests; in addition, the exact mechanism underlying the relationship with EPL and TA are unknown.

Significant increases in some CBC parameters, such as WBC (white blood cell) type, change during pregnancy, and a decrease in the ratio of granulocytes and T helper (Th) -1 lymphocytes, as well as a decrease in the ratio of Th-2 lymphocytes and monocytes, are observed in normal pregnancy conditions [17]. Macrophages and monocytes are of importance in the development of the placenta. Macrophages and monocytes promote the invasion of extravillous trophoblasts, spiral artery remodeling and the parturition process. On the other hand, there are controversial reports in published literature regarding the association of the deregulation of these cells with complications during pregnancy, such as abortion, preeclampsia and preterm labour [18].

MPV, which shows platelet activation and function, is measured as a maximum amplitude (EPL). MPV is a precise measure of the platelet size. Larger platelets have higher MPV values; therefore, higher MPV is more reactive and causes higher values of hemostatic prothrombotic factors [19]. Moreover, in a group of patients with maternal thrombophilia, hypercoagulability may lead to low perfusion of the placenta, and ultimately, this may cause loss of the fetus [19]. Kosus et al. found slightly increased EPL values for patient MPV. The researchers concluded that slightly increased MPV might encourage thrombosis [20]. On the other hand, some investigators suggested that MPV was significantly lower in patients with miscarriage compared to the control group [21]. In this study, MPV values were found to be significantly lower in EPLG than in TAG and HCG. It was concluded that due to inflammation and bleeding, platelets with higher activity (larger platelets) can migrate to the region in earlier gestational weeks, and this may lead to a decrease in MPV in maternal circulation in EPLG.

NLR is a marker that is important in inflammatory conditions. leukocyte types may vary depending on immune response. Neutrophil count values increase whereas lymphocyte counts decrease. NLR varies in various systemic inflammatory diseases. Various researchers have reported that there was an increase in the prognostic and predictive values of NLR in cases including colorectal and lung cancers, and in hepatocellular carcinoma [7]. In addition, significant changes were observed in NLR values for various conditions seen during pregnancy. Kurtoglu et al. [22] reported high NLR values in preeclampsia. Similarly, significant changes were observed in NLR values in gestational diabetes, intrahepatic cholestasis and hyperemesis gravidarum [11, 12, 14]. In the present study, the relationship between NLR, EPL and TA were not found to be significant.

PLR is another marker used to analyze thromboembolic events, inflammatory diseases and malignancies. It

Table 2. Prognostic values of optimum cut-offs for first trimester neutrophils count, lymphocytes count, platelet count, mean platelet volüme, neutrophils-lymphocytes ratio and platelets-lymphocytes ratio in predicting early pregnancy loss and threatened abortion

Table 2a

Early pregnancy loss	Cut off	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
Hemoglobin [g/dL]	≤ 12.3	42.00	28.2–56.8	80.00	66.3–90.0	2.10	1.1–4.0	0.73	0.6–1.0	67.7	52.5–80.0	58.0	51.2–64.5
Lymphocytes [10^3 uL]	≤ 22.3	52.00	37.4–66.3	68.00	53.3–80.5	1.63	1.0–2.6	0.71	0.5–1.0	61.9	50.0–72.5	58.6	50.1–66.7
MPV [fL. mean±SD]	≤ 9.6	88.00	75.7–95.5	88.00	75.7–95.5	7.33	3.4–15.6	0.14	0.06–0.3	88.0	77.5–94.0	88.0	77.5–94.0
Neutrophils [10^3 uL]	> 68.9	58.00	43.2–71.8	66.00	51.2–78.8	1.71	1.1–2.7	0.64	0.4–0.9	63.0	52.0–72.8	61.1	51.8–69.7
NLR	> 2.99	56.00	41.3–70.0	68.00	53.3–80.5	1.75	1.1–2.8	0.65	0.4–0.9	63.6	52.2–73.7	60.7	51.7–69.0
Platelets [10^3 uL]	≤ 197	18.00	8.6–31.4	92.00	80.8–97.8	2.25	0.7–6.8	0.89	0.8–1.0	69.2	42.6–87.2	52.9	49.0–56.7
PLR	> 115.41	78.00	64.0–88.5	50.00	35.5–64.5	1.56	1.1–2.1	0.44	0.2–0.8	60.9	53.3–68.1	69.4	55.7–80.4
RBCs [10^6 uL]	≤ 4.57	46.00	31.8–60.7	76.00	61.8–86.9	1.92	1.1–3.4	0.71	0.5–1.0	65.7	51.8–77.3	58.5	51.1–65.5

Table 2b

Threatened abortion	Cut off	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	-LR	95% CI	+PV	95% CI	-PV	95% CI
Hemoglobin [g/dL]	≤ 13.9	92.00	80.8–97.8	24.00	13.1–38.2	1.21	1.0–1.4	0.33	0.1–1.0	54.8	50.4–59.1	75.0	50.9–89.7
Lymphocytes [10^3 uL]	≤ 24.2	58.00	43.2–71.8	62.00	47.2–75.3	1.53	1.0–2.3	0.68	0.5–1.0	60.4	49.9–70.0	59.6	50.0–68.6
MPV [fL. mean±SD]	≤ 9.7	40.00	26.4–54.8	84.00	70.9–92.8	2.50	1.2–5.1	0.71	0.6–0.9	71.4	54.9–83.7	58.3	52.0–64.4
Neutrophils [10^3 uL]	> 67.5	62.00	47.2–75.3	58.00	43.2–71.8	1.48	1.0–2.2	0.66	0.4–1.0	59.6	50.0–68.6	60.4	49.9–70.0
NLR	> 2.91	52.00	37.4–66.3	66.00	51.2–78.8	1.53	1.0–2.4	0.73	0.5–1.0	60.5	48.9–71.0	57.9	49.2–66.1
Platelets [10^3 uL]	≤ 287	80.00	66.3–90.0	40.00	26.4–54.8	1.33	1.0–1.7	0.50	0.3–1.0	57.1	50.6–63.5	66.7	51.1–79.3
PLR	> 178.72	20.00	10.0–33.7	98.00	89.4–99.9	10.00	1.3–75.2	0.82	0.7–0.9	90.9	57.1–98.7	55.1	51.5–58.6
RBCs [10^6 uL]	≤ 4.45	54.00	39.3–68.2	84.00	70.9–92.8	3.37	1.7–6.7	0.55	0.4–0.8	77.1	63.0–87.0	64.6	56.9–71.6

CI — confidence interval; LR+ — positive likelihood ratio; LR– — negative likelihood ratio; MPV — mean platelet volume; -PV — negative predictive3 value; +PV — positive predictive value

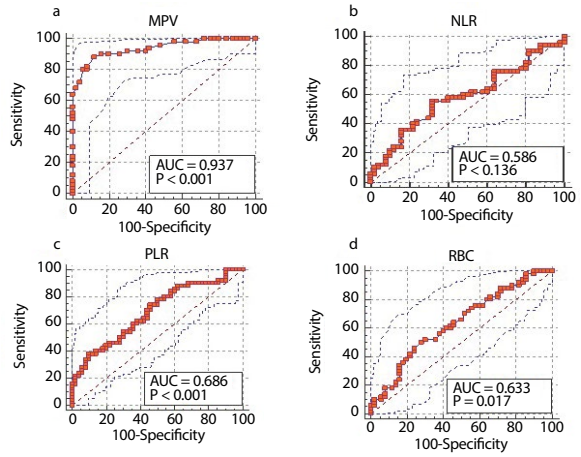

Figure 1. ROC analysis performed to investigate the effect of MPV, NLR, PLR, RBC value in predicting early pregnancy loss; MPV — mean platelet volume; NLR — neutrophils-lymphocytes ratio; PLR — platelets-lymphocytes ratio; RBC — red blood cell

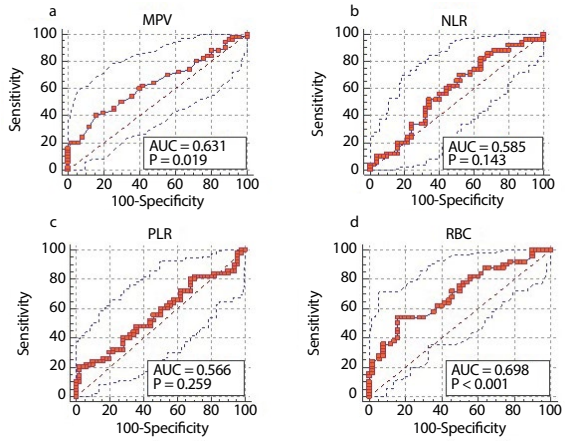

Figure 2. ROC analysis performed to investigate the effect of MPV, NLR, PLR, RBC value in predicting threatened abortion; MPV — mean platelet volume; NLR — neutrophils-lymphocytes ratio; PLR — platelets-lymphocytes ratio; RBC — red blood cell

has been reported that there is a significant relationship between the increase in PLR and major side effects in cardiovascular diseases and the decrease in the survival rate in some malignancies [23, 24]. PLR has been previously examined in pregnancy-related issues such as gestational diabetes, preeclampsia, pancreatitis and early premature rupture of membranes (PPROM) [12, 13, 25]. Endothelial dysfunction and the increase in elevated PLR can be associated with an increase in hemostatic functions which lead to the thrombosis of spiral arterioles. In another study, it has been stated that platelet activation is of utmost importance in the etiopathogenesis of arterial occlusion and could also lead to injury to the endothelium, consequently, leading to an increase in thromboxane A2 values [26]. Tola EN. found a negative relationship between PLR and embryonic implantation. They explained this through thrombosis of spiral arterioles [27]. Our study is the first to show that PLR is an important predictor of EPL and TA. In the current study, PLR was higher in EPLG and TAG (148.01 ± 38.24 vs 122.9 ± 29.65, 134.26 ± 42.51 vs 122.9 ± 29.65 for $p < 0.001$, respectively) (Tab. 1).

A small sample size and lack of a power calculation constitute the inherent limitations of the present study. In addition, the fact that the research uses a retrospective design and its use of data from a single tertiary medical centre limits extrapolation of the results to the general population. In spite of these limitations, this study is the first that investigates the relationship between CBC inflammation markers, and EPL and TA.

CONCLUSIONS

MPV, RBCs and PLR values were associated with first-trimester miscarriage. These platelet indices, which are not expensive and are easy-to-apply, can be used to predict fetal losses. Future studies on this subject should focus on randomized, prospective, controlled trials carried out on a larger subject group to obtain more precise conclusions.

Conflict of interest

The authors declare no conflicts of interests.

This work complies with ethical standards and the Helsinki Declaration.

REFERENCES

1. Jauniaux E, Burton GJ. Pathophysiology of histological changes in early pregnancy loss. Placenta. 2005; 26(2-3): 114–123, doi: 10.1016/j.placenta.2004.05.011, indexed in Pubmed: 15708112.
2. Clark DA, Coulam CB, Daya S, et al. Unexplained sporadic and recurrent miscarriage in the new millennium: a critical analysis of immune mechanisms and treatments. Hum Reprod Update. 2001; 7(5): 501–511, doi: 10.1093/humupd/7.5.501, indexed in Pubmed: 11556498.
3. Burgoyne PS, Holland K, Stephens R. Incidence of numerical chromosome anomalies in human pregnancy estimation from induced and spontaneous abortion data. Hum Reprod. 1991; 6(4): 555–565, doi: 10.1093/oxfordjournals.humrep.a137379, indexed in Pubmed: 1918307.
4. King A. Uterine leukocytes and decidualization. Hum Reprod Update. 2000; 6(1): 28–36, doi: 10.1093/humupd/6.1.28, indexed in Pubmed: 10711827.
5. Dosiou C, Giudice LC. Natural killer cells in pregnancy and recurrent pregnancy loss: endocrine and immunologic perspectives. Endocr Rev. 2005; 26(1): 44–62, doi: 10.1210/er.2003-0021, indexed in Pubmed: 15689572.
6. Gezer C, Ekin A, Ertas IE, et al. High first-trimester neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are indicators for early diagnosis of preeclampsia. Ginekol Pol. 2016; 87(6): 431–435, doi: 10.5603/GP.2016.0021, indexed in Pubmed: 27418220.
7. Ethier JL, Desautels DN, Templeton AJ, et al. Is the neutrophil-to-lymphocyte ratio prognostic of survival outcomes in gynecologic cancers? A systematic review and meta-analysis. Gynecol Oncol. 2017; 145(3): 584–594, doi: 10.1016/j.ygyno.2017.02.026, indexed in Pubmed: 28222899.
8. Verit FF, Cetin O, Yildirim O, et al. Neutrophil to lymphocyte ratio is superior to platelet to lymphocyte ratio as an early predictor of moderate/severe ovarian hyperstimulation syndrome. J Obstet Gynaecol. 2014; 34(7): 639–643, doi: 10.3109/01443615.2014.920792, indexed in Pubmed: 24911966.
9. Ilhan G, Atmaca FF, Altan E, et al. Evaluation of Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Red Blood Cell Distribution

Width-Platelet Ratio for Diagnosis of Premature Ovarian Insufficiency. J Family Reprod Health. 2016; 10(4): 211–216, indexed in Pubmed: 28546821.
10. Cho S, Cho H, Nam A, et al. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. Fertil Steril. 2008; 90(6): 2073–2079, doi: 10.1016/j.fertnstert.2008.03.061, indexed in Pubmed: 18555226.
11. Caglayan EK, Engin-Ustun Y, Gocmen AY, et al. Is there any relationship between serum sirtuin-1 level and neutrophil-lymphocyte ratio in hyperemesis gravidarum? J Perinat Med. 2016; 44(3): 315–320, doi: 10.1515/jpm-2015-0178, indexed in Pubmed: 26352076.
12. Sargın MA, Yassa M, Taymur BD, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios: are they useful for predicting gestational diabetes mellitus during pregnancy? Ther Clin Risk Manag. 2016; 12: 657–665, doi: 10.2147/TCRM.S104247, indexed in Pubmed: 27217758.
13. Serin S, Avcı F, Ercan O, et al. Is neutrophil/lymphocyte ratio a useful marker to predict the severity of pre-eclampsia? Pregnancy Hypertens. 2016; 6(1): 22–25, doi: 10.1016/j.preghy.2016.01.005, indexed in Pubmed: 26955767.
14. Kirbas A, Biberoglu E, Daglar K, et al. Neutrophil-to-lymphocyte ratio as a diagnostic marker of intrahepatic cholestasis of pregnancy. Eur J Obstet Gynecol Reprod Biol. 2014; 180: 12–15, doi: 10.1016/j.ejogrb.2014.05.042, indexed in Pubmed: 24997423.
15. Sacks GP, Seyani L, Lavery S, et al. Maternal C-reactive protein levels are raised at 4 weeks gestation. Hum Reprod. 2004; 19(4): 1025–1030, doi: 10.1093/humrep/deh179, indexed in Pubmed: 14990546.
16. Fang Y, Yu S, Ma Y, et al. Association of Dll4/notch and HIF-1a -VEGF signaling in the angiogenesis of missed abortion. PLoS One. 2013; 8(8): e70667, doi: 10.1371/journal.pone.0070667, indexed in Pubmed: 23950980.
17. Yuan M, Jordan F, McInnes IB, et al. Leukocytes are primed in peripheral blood for activation during term and preterm labour. Mol Hum Reprod. 2009; 15(11): 713–724, doi: 10.1093/molehr/gap054, indexed in Pubmed: 19628509.
18. Daglar HK, Kirbas A, Kaya B, et al. The value of complete blood count parameters in predicting preterm delivery. Eur Rev Med Pharmacol Sci. 2016; 20(5): 801–805, indexed in Pubmed: 27010132.
19. Alonso A, Soto I, Urgellés MF, et al. Acquired and inherited thrombophilia in women with unexplained fetal losses. Am J Obstet Gynecol. 2002; 187(5): 1337–1342, doi: 10.1067/mob.2002.126849, indexed in Pubmed: 12439528.
20. Kosus N, Kosus A, Yildirim M, et al. Mean platelet volume as a marker of thrombosis in patients with missed abortion. Acta Haematol. 2011; 125(4): 208–209, doi: 10.1159/000322943, indexed in Pubmed: 21252498.
21. Kaplanoglu M, Yuce T, Bulbul M. Decreased mean platelet volume is associated with the developing stage of fetoplacental unit in spontaneous abortion. Int J Clin Exp Med. 2015; 8(7): 11301–11306, indexed in Pubmed: 26379939.
22. Kurtoglu E, Kokcu A, Celik H, et al. May ratio of neutrophil to lymphocyte be useful in predicting the risk of developing preeclampsia? A pilot study. J Matern Fetal Neonatal Med. 2015; 28(1): 97–99, doi: 10.3109/14767058.2014.905910, indexed in Pubmed: 24635498.
23. Nording HM, Seizer P, Langer HF. Platelets in inflammation and atherogenesis. Front Immunol. 2015; 6: 98, doi: 10.3389/fimmu.2015.00098, indexed in Pubmed: 25798138.
24. Zhou X, Du Y, Huang Z, et al. Prognostic value of PLR in various cancers: a meta-analysis. PLoS One. 2014; 9(6): e101119, doi: 10.1371/journal.pone.0101119, indexed in Pubmed: 24968121.
25. Ekin A, Gezer C, Taner CE, et al. Risk factors and perinatal outcomes associated with latency in preterm premature rupture of membranes between 24 and 34 weeks of gestation. Arch Gynecol Obstet. 2014; 290(3): 449–455, doi: 10.1007/s00404-014-3227-3, indexed in Pubmed: 24695905.
26. Gasparyan AY, Ayvazyan L, Mikhailidis DP, et al. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011; 17(1): 47–58, doi: 10.2174/138161211795049804, indexed in Pubmed: 21247392.
27. Tola EN. The association between in vitro fertilization outcome and the inflammatory markers of complete blood count among nonobese unexplained infertile couples. Taiwan J Obstet Gynecol. 2018; 57(2): 289–294, doi: 10.1016/j.tjog.2018.02.019, indexed in Pubmed: 29673675.