

# Evaluation of inflammatory markers in threatened abortions and spontaneous abortions

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## ABSTRACT

**Objectives:** To evaluate the relationship between threatened abortion and inflammation markers such as procalcitonin, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio.

**Material and methods:** This was a prospective, controlled study. Serum procalcitonin, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) results of 60 threatened abortions were compared with the results of 60 spontaneous abortions and 60 healthy pregnancies. ROC analyses of procalcitonin, NLR and PLR were performed for threatened abortions. In addition, the threatened abortion group with ongoing pregnancy was divided into two groups according to the presence of hemorrhage area in ultrasonography and re-evaluated in terms of serum procalcitonin levels, NLR and PLR.

**Results:** Procalcitonin and NLR levels were significantly higher in the threatened abortion group than the abortion and control groups ( $p < 0.05$ ). There was no significant difference between the control and abortion groups. The area under the curve in ROC analysis was within the 95% confidence interval for procalcitonin and NLR and was statistically significant ( $p < 0.05$ ). Among the abortus imminens, which were divided into two groups according to whether there was hemorrhage area on ultrasonography, procalcitonin, NLR and PLR were higher in patients with bleeding area than without bleeding, but this was not significant ( $p > 0.05$ ).

**Conclusions:** There is an association between procalcitonin and NLR and threatened abortion. Procalcitonin and NLR may support the diagnosis of threatened abortion.

**Key words:** abortion; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio; procalcitonin; threatened abortions

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## INTRODUCTION

Threatened abortion is defined as uterine bleeding without cervical dilation up to the first 20 weeks of pregnancy. It occurs in 16–25% of pregnancies [1]. Only 50% of threatened abortion cases can be treated with current conservative methods. At the end of the first trimester, bleeding in 95–98% of pregnancies with a positive heartbeat by ultrasonography can occur up to the 20<sup>th</sup> gestational week [2].

Although the etiology of threatened abortion is unknown, there are many hypotheses put forward. Among these hypotheses, it is thought that threatened abortion is triggered by various mechanisms and causes obstetric and neonatal complications in the later stages of pregnancy [2]. One of the hypotheses put forward in threatened abortion is that intrauterine bleeding results from the disruption of the contractile-relaxing mechanisms of the uterus by various

uterotonic mediators [3]. The other hypothesis is that a chronic inflammatory reaction develops in the decidua with bleeding. According to this hypothesis, it is stated that this chronic inflammation causes placental development disorders in the later stages of pregnancy and causes obstetric complications (such as preterm labor, premature-preterm rupture of membranes and preeclampsia) [4].

Procalcitonin is the precursor of the calcitonin hormone and is present at undetectable levels in healthy individuals. Its level increases with cytokines released with bacterial infection [5]. In addition, it has been shown that the level is significantly increased in many diseases in which the inflammation process plays a role (end-stage renal disease, congestive heart failure, cirrhosis, acute kidney injuries, intracerebral hemorrhages, post-operative anastomotic leaks) [6–8].

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Like neutrophils, platelets increase the secretion of cytokines at the onset of inflammation, and increased cytokines contribute to the increase in inflammation by increasing the synthesis of new neutrophils and platelets. Like NLR, PLR shows a significant relationship with cancer and inflammatory diseases [9].

### Objectives

Since chronic inflammation is thought to play a role in the pathophysiology of threatened abortion, we wanted to evaluate the relationship between threatened abortions and inflammation markers such as procalcitonin, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in this study.

### MATERIAL AND METHODS

Ethical approval for this study was obtained from the Ethics Committee of Amasya University (protocol #121). The results of 60 patients diagnosed with threatened abortion who came to the Amasya Sabunçuoğlu Şerefeddin Training and Research Hospital Gynecology and Obstetrics Clinic between 15 June 2020 and 15 August 2021 were compared with the results of 60 patients who spontaneously aborted after threatened abortion diagnosis and 60 healthy pregnancies. The threatened abortion group was formed from pregnant women who were diagnosed with threatened abortion between six weeks and 20 weeks with vaginal bleeding but no cervical dilation. The abortion group was formed from those who were diagnosed with threatened abortion and then spontaneously aborted. The control group consisted of 60 healthy pregnancies between six and 20 weeks who came to the outpatient clinic for normal controls. Those with hypertension, diabetes, thrombophilia, those diagnosed with hyperemesis gravidarum, those with autoimmune, renal, cardiac or hepatic disease, those with a history of threatened abortion, preeclampsia, gestational diabetes, hellp syndrome in previous pregnancy, those with diseases that may trigger inflammation (such as infectious diseases, collagen tissue disease) and those with fetal anomalies were not included in the study and control groups. Pregnant women with positive fetal cardiac activity and diagnosed with threatened abortion were included in the study. Those with no positive fetal cardiac activity were not included in the study. Pregnant women included in the study with the diagnosis of threatened abortion were not re-evaluated in their subsequent vaginal bleeding. Pregnant women who met the study criteria for threatened abortion, and abortion and control groups were included in the study after they were informed about the study and their consent was obtained.

A Mindray DC-7 ultrasound device was used in the evaluation of pregnancy in the study. Obstetric ultrasonography was performed by a single clinician (S.M.A.).

The week of pregnancies, their development, fetal cardiac activity, whether amniotic fluids were normal or not, and whether there was a hemorrhage area around the gestational sac were evaluated by ultrasonography. Age, parity, height, weight, last menstrual period, education level, previous surgery, and whether they had chronic diseases were questioned in terms of demographic characteristics of all three groups. A blood sample was taken into a hemogram tube to evaluate serum neutrophils, lymphocytes, platelets, NLR and PLR, and into a biochemistry tube to evaluate parameters such as procalcitonin, liver and renal functions. In total, blood samples were taken into two separate tubes. Blood samples were taken within the first two hours after spontaneous abortions or diagnosis of threatened abortion.

Neutrophil, lymphocyte and platelet levels were evaluated with laser optics (X N-1000, Siemens, Japan) and procalcitonin with electrochemiluminescence immunoassay (Cobas e 411, Roche, Japan).

The groups were compared in terms of serum procalcitonin, neutrophil, lymphocyte and platelet levels, NLR and PLR. ROC analysis of procalcitonin, NLR and PLR was performed for threatened abortion. The threatened abortion group was divided in two according to the presence of hemorrhage area in ultrasonography and these two groups were also compared in terms of NLR, PLR and procalcitonin.

### Power analysis of the study

The sample size of the study was made with the G\*Power 3.1 program. It was calculated according to the effect width ( $d = 0.66$ ) and the two-tailed hypothesis method, considering that the incidence of threatened abortion was 16–25% in the study of Farrell et al. [1] and the number of women who gave birth in 2020 in the health institution where the research was conducted ( $n = 2154$ ). It was determined as  $1-\beta = 0.95$  and  $\alpha = 0.05$ . As a result of the calculation, it was determined that there should be 60 women for the control group, 60 women for the experimental group, and a total of 120 women.

### Statistical analysis

Data were analyzed with IBM SPSS V23 program. Conformity to normal distribution was examined with Kolmogorov-Smirnov test. Chi-square test and Fisher's Exact test were used to compare categorical variables according to groups. Mann-Whitney U test was used for comparing non-normally distributed data according to paired groups and independent two sample t-test was used for comparison of normally distributed data. One-way analysis of variance (ANOVA) was used to compare normally distributed data for three or more groups, and Kruskal Wallis test was used for non-normally distributed data. ROC analysis

**Table 1. Demographic characteristics of the groups**

		Threatened abortion n = 60	Spontaneous abortion after threatened abortion n = 60	Healthy pregnancies n = 60	p-value
Age [year]		27.38 ± 5.75	29.58 ± 5.52	28.17 ± 6.29	0.1118
Height [cm]		161.62 ± 5.12	162.23 ± 5.91	160.17 ± 6.06	0.130
Weight [cm]		64.38 ± 12.46	69.38 ± 16.09	66.07 ± 14.38	0.156
BMI [kg/m <sup>2</sup> ]		24.76 ± 5.30	26.38 ± 5.95	25.76 ± 5.49	0.280
Parity	Nulliparity	29 (48.3%)	25 (41.7%)	23 (38.3%)	0.530
	Multiparity	31 (51.7%)	35 (58.3%)	37 (61.7%)	
Education	Primer school	6 (10.0%)	11 (18.3%)	11 (18.3%)	0.388
	Midlee school	16 (26.7%)	23 (38.4%)	17 (28.4%)	
	High school	18 (30.0%)	12 (20.0%)	18 (30.0%)	
	Univercity	20 (33.3%)	14 (23.3%)	14 (23.3%)	
Previous operation	Yes	14 (23.3%)	17 (28.3%)	11 (18.3%)	0.432
	No	46 (76.7%)	43 (71.7%)	49 (81.7%)	
Chronic disease	Yes	67 (11.7%)	5 (8.3%)	3 (5.0%)	0.418
	No	53 (88.3%)	55 (91.7%)	57 (95.0%)	
Diagnosis week (week)		9.69 ± 3.80	10.11 ± 3.51	10.59 ± 11.16	0.784

P-values were calculated with the One-Way ANOVA Test (age, height, weight, BMI, diagnosis week) and Chi-square test

**Table 2. Comparison of procalcitonin, neutrophil, lymphocyte, platelet, NLR and PLR of the groups**

	Threatened abortion n = 60	Spontaneous abortion after threatened abortion n = 60	Healthy pregnancies n = 60	p-value
Procalcitonin [ng/mL]	0.050 ± 0.011 <sup>a</sup>	0.042 ± 0.013 <sup>b</sup>	0.041 ± 0.015 <sup>b</sup>	< 0.001
Neutrophil [ $\times 10^9/L$ ]	6.40 ± 1.79	6.00 ± 1.92	5.79 ± 1.24	0.130
Lymphocyte [ $\times 10^9/L$ ]	2.28 ± 1.76	2.28 ± 0.72	2.24 ± 0.64	0.974
Platelet [ $\times 10^9/L$ ]	236.90 ± 48.21	252.78 ± 52.25	249.91 ± 51.97	0.193
NLR	3.17 ± 1.01 <sup>a</sup>	2.76 ± 0.95 <sup>b</sup>	2.72 ± 0.74 <sup>b</sup>	0.012
PLR	121.56 ± 44.62	122.23 ± 47.0	120.04 ± 41.38	0.962

One Way ANOVA Test was used. <sup>a,b</sup> — there is no difference between groups with the same letter  
NLR — Neutrophil Lymphocyte Ratio; PLR — Platelet Lymphocyte Ratio

was used to determine the cut-off values for procalcitonin, NLR and PLR for threatened abortion. The significance level was  $p < 0.05$ .

## RESULTS

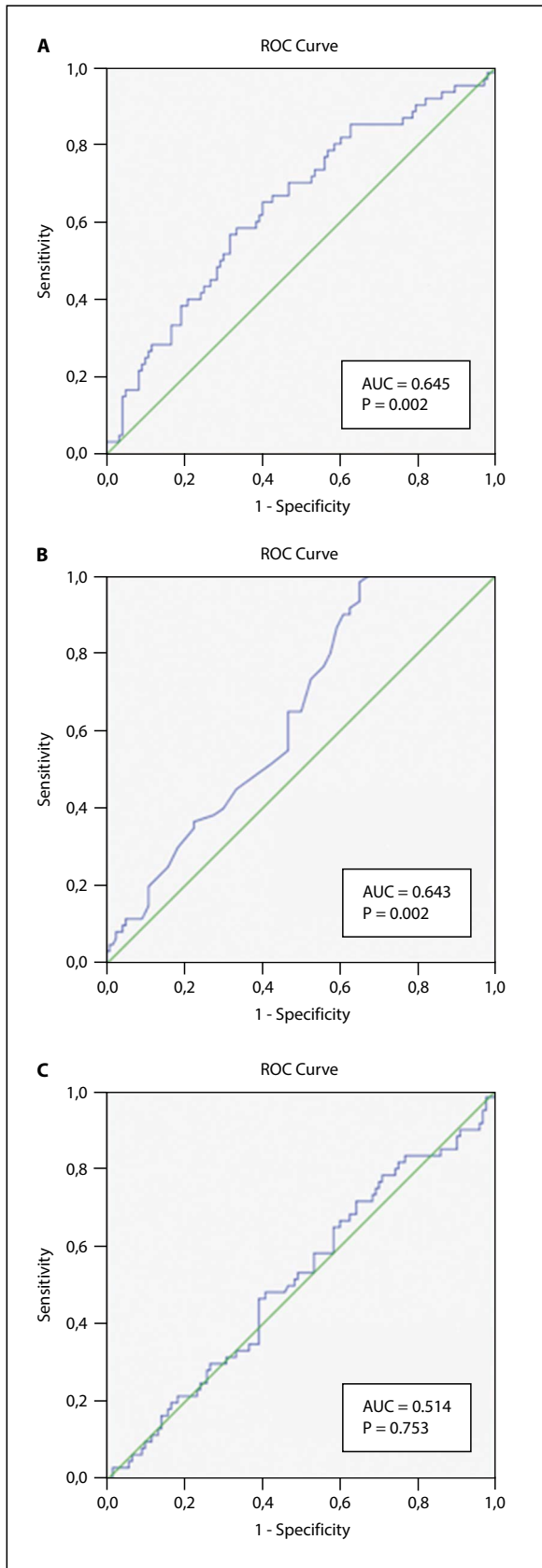
The groups were homogeneous in terms of demographic characteristics ( $p > 0.05$ ) (Tab. 1).

Serum procalcitonin level and NLR were significantly higher in the threatened abortion group than in the control and abortion groups ( $p < 0.05$ ). There was no significant difference between the control and abortion groups in terms of these parameters ( $p > 0.05$ ). There was no significant difference between the groups in terms of PLR, neutrophils, lymphocytes and platelets ( $p > 0.05$ ) (Tab. 2).

Serum procalcitonin levels, NLR and PLR for threatened abortions were evaluated by ROC analysis (Tab. 3).

In the ROC curve for procalcitonin and NLR, the area under the curve (AUC) was within the 95% confidence interval and was statistically significant ( $p < 0.05$ ) (Fig. 1). Procalcitonin and NLR can therefore be used as suitable parameters for diagnostic decision making in predicting disease. In the ROC curve for PLR, the AUC was not within the 95% confidence interval and was not statistically significant ( $p > 0.05$ ) (Fig. 1).

The threatened abortion group was divided into two groups according to the presence or absence of hemorrhage area on ultrasonography and compared in terms of serum procalcitonin levels, NLR and PLR. Serum procalcitonin levels, NLR and PLR values were higher in those with hemorrhage areas on ultrasonography than those without, but there was no significant difference between the groups ( $p > 0.05$ ) (Tab. 4).



**Figure 1.** A. ROC curve for procalcitonin; B. ROC curve for NLR; C. ROC curve for PLR

## DISCUSSION

In our study, we evaluated the relationship between procalcitonin, NLR and PLR, which are known inflammatory markers, and threatened abortion due to the chronic inflammatory reaction, which is one of the hypotheses suggested to play a role in the pathophysiology of threatened abortion. For this purpose, we compared the results of 60 threatened abortions with results of 60 spontaneous abortions (after threatened abortion diagnosis) and 60 healthy pregnancies.

In many studies, it has been shown that various obstetric and neonatal complications develop in the later stages of pregnancy due to threatened abortion [4, 10]. The reason for this is that the pathological mechanism that usually causes the underlying threatened abortion causes these various complications in the later stages of pregnancy. If the pathophysiological mechanism causing threatened abortion becomes clear, these complications secondary to threatened abortion could be prevented. For example, in a meta-analysis including 31 studies, it was stated that first trimester bleeding causes very important obstetric complications such as prematurity, intrauterine growth retardation and increased risk of perinatal death [10]. Most of these complications are conditions that increase maternal and fetal morbidity and mortality. Predicting these complications that may occur due to threatened abortion and taking the necessary precautions will reduce this maternal-fetal morbidity and mortality, and thus reduce the cost spent on this issue [11]. One of the hypotheses put forward in the pathophysiology of threatened abortion is the development of a chronic inflammatory reaction in the decidua with bleeding [4]. Inflammation of the fetus or placenta may cause an inflammatory response in the mother [12]. Therefore, in this study, we wanted to evaluate the levels of procalcitonin, NLR and PLR, which are known inflammatory markers and have been shown to be related to diseases based on chronic inflammation, in patients with threatened abortion and spontaneous abortion.

The normal level of procalcitonin is  $< 0.5$  ng/mL [13]. Procalcitonin is produced in large quantities, especially by macrophages and monocytic cells, by up-regulation of the CALC-1 gene, mostly in bacterial infections. The rise of procalcitonin occurs immediately due to its cytokine-like behavior [14]. It reaches a detectable level in 2–3 hours, peaking at the sixth hour. Procalcitonin is also elevated in various non-infectious conditions such as cirrhosis, pancreatitis, mesenteric infraction, burns and aspiration pneumonia [15, 16]. Studies differ in what appropriate negative cut-off points should be used for procalcitonin [15, 17]. For example, serum procalcitonin levels above 0.06 ng/mL in acute heart failure, and in another study, serum procalci-

**Table 3. Sensitivity, specificity, positive predictive and negative predictive values for procalcitonin, NLR, and PLR**

	Area	P	Cutt-off	Lower	Upper	Sensitivity	Specificity	PPV	NPV
Procalcitonin	0.645	0.002	0.048500	0.565	0.725	0.550	0.467	83.5	65.1
NLR	0.643	0.002	2.8083	0.557	0.729	0.600	0.392	85.0	68.2
PLR	0.514	0.753	114,9604	0.425	0.604	0.517	0.483	73.2	59.7

p-values were calculated according to ROC analysis; NPV — negative predictive value; PPV — positive predictive value

**Table 4. Comparison of the two groups formed by separating the threatened abortions as with and without hemorrhage area on ultrasound in terms of procalcitonin, NLR and PLR**

	Threatened abortions with hemorrhage area on ultrasound n = 11	Threatened abortions without hemorrhage area on ultrasound n = 49	p-value
Procalcitonin [ng/mL]	0.053 ± 0.004	0.050 ± 0.012	0.117
NLR	3.48 ± 0.99	3.10 ± 1.00	0.257
PLR	135.19 ± 50.34	118.50 ± 43.21	0.266

Independent T Test and Mann-Whitney U test (procalcitonin) were used; NLR — neutrophil lymphocyte ratio; PLR — platelet lymphocyte ratio

tonin levels above 0.05 ng/mL in patients with cirrhosis were found to be significant [8, 18]. In our study, procalcitonin levels were significantly higher than in the abortion and control groups. They were at the same levels in the abortion group and the control group ( $0.050 \pm 0.011$ ,  $0.042 \pm 0.013$ ,  $0.041 \pm 0.015$  ng/mL, respectively). The significantly higher serum procalcitonin levels in the threatened abortions group confirms the hypothesis of chronic inflammation. The fact that the procalcitonin level was similar in the abortion group and the control group may suggest that this inflammation is impaired by abortion and therefore procalcitonin may be decreased. The half-life of procalcitonin of 24 hours may support this idea [19].

Studies have reported that serum procalcitonin levels differ according to the gestational week. In one study, serum procalcitonin level was 0.043 µg/L at 24–28 weeks of pregnancy, 0.061 µg/L at 36–40 weeks, 0.068 µg/L at birth, 0.200 µg/L on postpartum day 2–3, and 0.060 µg/L on postpartum day 10 [20].

In our study, we found the serum procalcitonin level to be  $0.041 \pm 0.015$  ng/mL in healthy pregnant women in the first trimester. In the threatened abortion group, it was  $0.050 \pm 0.011$  ng/mL and was significantly higher than the healthy pregnancy group. It was also statistically significant in the ROC analysis. In other words, procalcitonin can be used as a suitable parameter as a diagnostic decision maker in predicting threatened abortion. Serum procalcitonin levels were higher in the threatened abortion group with a hemorrhage area on ultrasonography compared to without, but this was not significant. The fact that the serum procalcitonin level was higher in the group with threatened abortion with a hemorrhage area may be due to the persis-

tence of bleeding for a certain period of time and increased triggering of the chronic inflammatory reaction [4].

Most of the studies on NLR and PLR in early pregnancy are studies that compare pregnancies that result in abortion with control groups, in order to evaluate the utility of these parameters as precursors of early miscarriages. In the literature, there is a rare study evaluating NLR and PLR in threatened abortion and spontaneous abortion (after threatened abortion). In the study of Ata et al. [21], NLR and PLR levels were compared between healthy pregnancies, threatened abortions and abortions at early gestational weeks. While there was no difference between the three groups in terms of NLR levels, PLR levels were found to be higher in early pregnancy loss and threatened abortions. In our study, NLR was significantly higher in the threatened abortion group compared to the abortion group and the control group. There was no significant difference between the groups in terms of PLR.

In a study in which NLR in abortions were compared with the first trimester NLR of patients who had a healthy delivery, no significant difference was found between the two groups [22]. While it was reported in another study that low NLR and PLR values were associated with early pregnancy losses, on the contrary, in another study, it was concluded that high PLR and NLR values were associated with early pregnancy losses [23, 24]. In our study, there was no significant difference in terms of NLR and PLR levels in the comparison of abortions with healthy pregnancies.

As in our study, there are other studies evaluating other biomarkers to confirm the presence of an inflammatory process in the etiopathogenesis of threatened abortion. Vascular endothelial growth factor (VEGF), soluble VEGF

receptor-1 (sVEGFR-1) and VEGF/sVEGFR-1 ratio were found to be associated with threatened abortion pathogenesis [25]. Apolipoprotein A-1, amniotic immune biomarkers (IL2 $\beta$  receptor, IL6, IL8, IL10, IL1 $\beta$  and TNF $\alpha$ ) have been associated with threatened abortions [26, 27]. A systematic review and meta-analysis of prospective studies have highlighted the role of the biochemical markers' serum progesterone, hCG, pregnancy associated plasma protein A, estradiol and cancer antigen 125 (CA 125) in the prediction of outcome in women with threatened miscarriage. According to the results of this review, serum CA 125 was determined as the marker with the highest predictive value in determining 'probable to continue' pregnancies. Although serum hCG and progesterone biomarkers are most used, they are not useful in predicting the outcome of a pregnancy with a viable fetus [28]. Low PAPP-A values in threatened abortion women is associated with pregnancy failure [29].

The fact that the number of cases in our study is equal to the number of cases detected in the power analysis can be considered as a limitation of the study. As a matter of fact, if the number of our cases were greater, it would have increased the power of our study. The strength of our study is the simultaneous evaluation of the relationship between both abortus imminens and abortions, and procalcitonin, NLR and PLR.

## CONCLUSIONS

In summary, in this study an association between procalcitonin and NLR and threatened abortion was found. This supports chronic inflammation having a role in the etiopathogenesis of threatened abortion. In addition, an increase in serum procalcitonin and NLR levels in pregnancies may indicate an increase in risk of threatened abortion, and in contrast, a decrease in serum procalcitonin and NLR in threatened abortions may herald spontaneous abortion.

### Conflict of interest

All authors declare no conflict of interest.

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