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Can the Systemic Immune-Inflammation Index (SII) Predict the Outcome of Threatened Miscarriage?

Sistemik İmmün-İnflamasyon İndeksi (SII) Düşük Tehdidinin Sonucunu Öngörebilir mi?

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ABSTRACT

AIM: Inflammatory markers have gained attention in recent years and the search continues for cost-effective, widely available, easily applicable, and interpretable biomarkers that can more accurately predict pregnancy outcomes. The study aims to determine a cut-off value for systemic immune-inflammation index (SII) (neutrophil × platelet /lymphocyte) in the prediction of the outcome of threatened miscarriage (TM).

MATERIAL AND METHOD: This retrospective case-control study was designed at the Obstetrics-Gynecology and Perinatology Clinics. Singleton pregnant women with TM who were followed up in the outpatient clinics or hospitalized and whose pregnancy resulted in our hospital were included in the study. Women whose pregnancies resulted in miscarriage were included in Group I. Women whose pregnancies resulted in childbirth were in Group II. Receiver operating characteristic (ROC) curves were used to assess the performance of inflammatory indices in predicting the outcome of TM.

RESULTS: A total of 730 pregnant women with the diagnosis of TM were included in the present study. There were 239 patients in Group I, and there were 491 patients in Group II. SII was statistically significantly higher in Group II (856.6 vs. 938.4; p<0.001), and the ROC curve produced a sensitivity of 31.8% and a specificity of 83.3%. The area under the curve (AUC) for the SII was 0.594 (95% CI: 55.8 to 63, p < 0.001).

CONCLUSION: Elevated SII in maternal blood in TM cases indicates an inflammatory process, but results in delivery. Clinicians should be cautious about SII values of ≤692/L (specificity of 83.3%) for miscarriage.

Keywords: Abortion; Pregnancy; Systemic immune-inflammation index; Threatened miscarriage

ÖZET

AMAÇ: Son yıllarda inflamatuar belirteçler ilgi görmeye başlamıştır ve gebelik sonuçlarını daha doğru bir şekilde tahmin edebilen maliyet etkin, yaygın olarak bulunabilen, kolayca uygulanabilir ve yorumlanabilir biyobelirteçler için arayış devam etmektedir. Bu çalışmanın amacı, düşük tehdidi (DT) sonucunun tahmininde sistemik immün-inflamasyon indeksi (SII) (nötrofil × trombosit/lenfosit) için bir kesme değeri belirlemektir.

GEREÇ VE YÖNTEM: Bu retrospektif vaka-kontrol çalışması adın Hastalıkları, Doğum ve Perinatoloji kliniğimizde tasarlanmıştır. Çalışmaya polikliniklerde takip edilen veya hastaneye yatırılan ve gebelikleri hastanemizde sonlanan DT'li tekil gebe kadınlar dahil edildi. Gebelikleri düşükle sonuçlanan kadınlar Grup I'e dahil edildi. Gebelikleri doğumla sonuçlanan kadınlar Grup II'ye dahil edildi. Receiver operating characteristic (ROC) eğrileri, TM sonucunu tahmin etmede inflamatuar indekslerin performansını değerlendirmek için kullanıldı.

BULGULAR: Bu çalışmaya DT tanısı almış toplam 730 gebe kadın dahil edildi. Grup I'de 239 hasta ve Grup II'de 491 hasta vardı. SII, Grup II'de istatistiksel olarak anlamlı derecede daha yüksekti (856.6'ya karşı 938.4; p<0.001) ve ROC eğrisi ile %31.8 duyarlılık ve %83.3 özgüllük saptandı. SII için eğri altında kalan alan (EAA) 0.594 idi (%95 CI: 55.8 ila 63, p < 0.001).

SONUÇ: DT olgularında maternal kandaki yüksek SII, inflamatuar bir süreci göstermekte ve doğumla sonuçlanmaktadır. Klinisyenler, düşük için ≤692/L (özgüllük %83.3) SII değerleri konusunda dikkatli olmalıdır.

Anahtar Kelimeler: Abort; Düşük tehdidi; Gebelik; Sistemik immün-inflamasyon indeksi

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INTRODUCTION

Threatened miscarriage (TM) is a term that is defined as vaginal bleeding or spotting without cervical changes before the 24th gestational week of pregnancy or with a fetus weighing less than 500g (1,2). TM is associated with adverse outcomes in the following weeks of pregnancy and in about 50% of these cases, a miscarriage occurs despite therapeutic precautions (3).

A history of miscarriage, stillbirth, or congenital anomalies in a previous pregnancy increases the risk of fetal loss among patients presenting with first-trimester hemorrhage (4). In patients with an established history of prior miscarriage, the probability of subsequent miscarriage is estimated to be 20% (5). With the occurrence of three consecutive instances of miscarriage, the risk is observed to increase to 50% (5). Furthermore, maternal systemic diseases, including diabetes mellitus and thyroid dysfunction, infertility treatments, maternal and paternal genetic defects, and advanced maternal and paternal age are identified as risk factors for spontaneous miscarriage (5-9). Although some fetal and maternal factors are thought to be responsible for its etiology, the exact pathophysiological process has yet to be elucidated (10). It is, however, thought to be a multifactorial process. One of the most crucial phases for the successful development of the embryonic gestational sac is the invasion of trophoblast cells into the maternal decidua in the first trimester (10). A reduction or alteration in the capacity of the vascular system to invade is one of the factors that contribute to the development of preeclampsia and fetal growth restriction (11).

Although many biochemical markers such as serum levels of human chorionic gonadotropin, progesterone, estradiol, pregnancy-associated plasma protein A, cancer antigen 125 (CA125), human placental lactogen, alpha-fetoprotein, inhibin A, follistatin, and activin A, have been studied to predict the outcome of TM, these markers are considered unreliable (12). It is widely acknowledged that processes associated with systemic inflammatory regulation exert a significant influence on the course of pregnancy. It is imperative to acknowledge the significance of the suppression of the inflammatory response in facilitating the acceptance of semi-allogeneic embryos. A pivotal aspect of the immune response that undergoes significant alterations during pregnancy is the systemic immune response. Inflammatory markers during pregnancy have become a focus of interest in recent years.

The systemic immune inflammation index (SII) is a novel index based on peripheral lymphocyte (LYM), neutrophil (NEUT), and platelet (PLT) counts, reflecting the balance between inflammation and the immune response. The SII has been utilised in select studies to predict adverse pregnancy outcomes (13). The objective of this study was to evaluate the clinical significance of the SII in predicting pregnancy outcomes in patients with TM.

MATERIAL AND METHOD

This retrospective study was designed at the Obstetrics-Gynecology and Perinatology Clinics of Etlik Zubeyde Hanim Women's Health Education and Training Hospital between January 2017 and January 2020. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and received approval from the local ethics committee (April 21, 2022; no: 05/2022).

Singleton pregnancies over the age of 18 with a diagnosis of TM between the gestational week of six to 12 weeks with fetal heartbeat were included in the study. The study excluded women who exhibited any of the following risk factors or conditions: maternal co-morbid diseases, inflammatory conditions (presence of autoimmune and/or chronic inflammatory disease; the presence of infection (especially upper or lower respiratory tract infection, pelvic inflammatory disease, urinary tract infection, and active or non-active coronavirus or influenza infection etc.); all conditions that may affect the immune system (such as corticosteroid, anti-oxidant or anti-inflammatory drug use, smoking, liver and/or kidney disease, presence of cancer); presence of cardiovascular disease (hypertension, coronary artery disease, hyperlipidemia).

Singleton pregnant women with TM who were hospitalized and whose pregnancy resulted in (miscarriage or the birth of a healthy child) at our hospital were included in the study. Women whose pregnancies resulted in miscarriage were included in Group I. Women whose pregnancies resulted in childbirth were in Group II. The data of both groups such as demographic information (age, gravidity, and parity); first trimester complete blood count (CBC) test; ultra-sonographic findings (embryonic or fetal viability; the presence of sonographically detected subchorionic hemorrhage, etc.); gestational week in which TM was diagnosed; pregnancy outcomes and pregnancy complications were obtained from the patients' files or electronic hospital records.The flow chart illustrating the study's methodology is presented in

Figure 1: Flow Chart

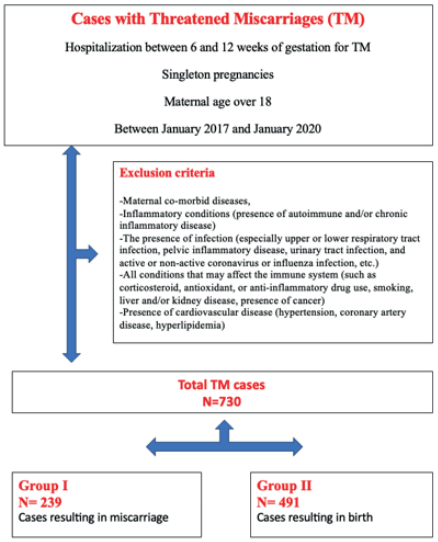

Figure 1. Flow Chart of the Study

We examined first-trimester CBC tests (NEUT, PLT, and LYM) in both groups on hospitalization and calculated SII (NEUT × PLT / LYM) (10^9 / L) (14). We compared the SII value of both groups to get the pregnancy results of women with TM. We used the ADVIA® 120 Hematology System (Siemens Healthcare Diagnostics Inc., Deerfield, IL) to analyze hemoglobin (HGB), hematocrit (HTC), NEUT, PLT, LYM, and monocyte (MONO) parameters. As the primary outcome, the SII value and other inflammatory markers obtained from the hemogram were compared in both groups, and as the secondary outcome, other parameters such as demographic and obstetric characteristics of the groups were compared.

Statistical analysis

All statistical analyses were conducted using the RStudio integrated development environment for statistical computing to examine the data (15). The variables were examined to determine whether they exhibited a normal distribution. This was carried out using both histograms and probability plots, as well as the Kolmogorov-Smirnov and Shapiro-Wilk tests. In cases where the numerical data exhibited a non-normal distribution, descriptive analyses were conducted using medians and quartiles (Q1-Q3). The objective was to facilitate the comparison of the parameters of the non-normal distributions across the groups, which was achieved through the use of the Mann-Whitney U test. In the case of categorical variables, the results were presented in descriptive form using frequencies and percentages. Relationships among categorical variables were analyzed using either the chi-square test or Fisher's exact test, as appropriate. The capacity of the various parameters to predict miscarriage was assessed through the utilization of receiver operating characteristic (ROC) curve analysis. In instances where a significant cut-off value was identified, the sensitivity, specificity, and area under the curve (AUC) value were presented, in addition to the positive likelihood ratio and the negative likelihood ratio. The ROC curves and areas under the curve of these parameters were compared with one another. To infer statistical significance, an overall 5% Type I error level was employed. A p-value of less than 0.05 was considered to indicate a statistically significant result.

RESULTS

A total of 730 pregnant women who presented with vaginal bleeding or spotting without cervical dilatation and were hospitalized with

Table 1. Demographic data of the patients

	Group I (n=239)	Group II (n=491)	Total (n=730)	*p* value
Age (years)	26 (22-32)	28 (24-33)	28 (23.75-32)	**0.001**
TM diagnosisweek	10 (6-13)	9(6-12)	9(6-12)	0.111
Hematoma size (length) (mm)	27 (19.5-41.5)	30(20-44)	30(20-44)	0.4
Hematomasize (width)(mm)	14 (11-20)	14(9-22)	14(10-21)	0.851
Gravidity (n)	1 (1-2)	2(2-3)	2(1-3)	**<0.001**
Parity (n)	0(0-0)	1(0-2)	0(0-1)	**<0.001**
WBC (x10^9/L)	8.615 (7.275-10.2075)	9.34 (7.985-10.875)	9.16 (7.685-10.64)	**<0.001**
HG (g/dL)	12.5 (11.7-13.2)	12.4 (11.7-13.1)	12.5 (11.7-13.2)	0.982
HTC (%)	37.8 (35.625-39.4)	37.5 (35.2-39.3)	37.6 (35.35-39.4)	0.441
PLT (x10^9/L)	257 (228-307)	276 (236-314)	269 (233-312)	**0.032**
MONO(x10^9/L)	0.4 (0.32-0.49)	0.42 (0.34-0.52)	0.42 (0.34-0.51)	**0.025**
NEUT (x10^9/L)	6.05 (4.76-7.31)	6.65 (5.43-8.09)	6.485 (5.2-7.7825)	**<0.001**
LYM (x10^9/L)	1.83 (1.59-2.28)	1.89 (1.49-2.28)	1.87 (1.5175-2.28)	0.725
NLR	3.1184 (2.36-4.1461)	3.41 (2.7426-4.4307)	3.3096 (2.6507-4.3568)	**<0.001**
PLR	138.6454 (115-176.506)	146.4481 (120.362-177.3973)	143.9231 (118.7724-176.8080)	0.087
MLR	0.2089 (0.1732-0.2582)	0.2243 (0.18-0.2801)	0.2182 (0.1776-0.2709)	**0.01**
SII	856.6 (625.6077-1125.6790)	938.4 (741.8692-1239.9328)	911.5 (716.0548-1206.0087)	**<0.001**

Abbreviations; n – number; WBC – white blood cells; HG – hemoglobin; HTC – hematocrit; PLT – platelet; MONO – monocyte; NEUT – neutrophil; LYM – lymphocyte; NLR – neutrophil / lymphocyte ratio; PLR – platelet / lymphocyte ratio; MLR – monocyte / lymphocyte ratio; SII – systemic immune-inflammation index; TM – threatened miscarriage;

p-value < 0.05

Non-parametric data was expressed with median and quartiles (Q1 – Q3)

There were no significant differences in the size of the subchorionic hematoma, gestational week in which TM was diagnosed, HGB – HTC values, LYM value, and PLT – LYM ratio (PLR) between the groups. Age, gravidity, parity, white blood count (WBC) value, PLT value, MONO value, NEUT value, NEUT – LYM ratio (NLR), and MONO – LYM ratio (MLR) values were statistically significant (p< 0.05).

In group II, the following pregnancy outcomes were found: Preterm birth in 19.6% of pregnancies, fetal growth restriction (FGR) in 10% of pregnancies, gestational hypertension in 9.2% of pregnancies, gestational diabetes in 4.7% of pregnancies, premature rupture of membranes (pPROM) in 4.5% of pregnancies, oligohydramnios in 3.7% of pregnancies, polyhydramnios in 2.6% of pregnancies, and placenta previa in 2.2% of pregnancies.

In ROC analysis, significant cut-off values for parameters were found with statistical significance between groups. In the ROC analysis of SII, WBC, PLT, MONO, NEUT, NLR, and MLR ratios were statistically significant (p: < 0.05).

Table 2. ROC curve analysis for assessing the performance of inflammatory markers in predictingpregnancy outcome

	AUC	CI 95%	*P* value	Cut-off value	Sensitivity (%)	Specificity (%)	+LR	-LR
SII	0.594	0.558-0.630	<0.001	≤692	31.8	83.3	1.90	0.82
WBC	0.589	0.552-0.626	<0.001	≤9.42	65.5	49.1	1.29	0.70
PLT	0.549	0.512-0.585	0.034	≤263	56.9	58.7	1.38	0.73
MONO	0.552	0.514-0.589	0.022	≤0.4	52.6	57.4	1.24	0.83
NEUT	0.601	0.565-0.637	<0.001	≤5.71	43.9	70.9	1.51	0.79
NLR	0.587	0.551-0.623	<0.001	≤2.53	30.9	85.4	2.11	0.81
MLR	0.560	0.522-0.597	0.008	≤0.21	55.6	55.9	1.26	0.79

Abbreviations; AUC – area under the curve; CI - confidence interval; LR - likelihood ratio; WBC – white blood cells; PLT – platelet; MONO – monocyte; NEUT – neutrophil; NLR – neutrophil / lymphocyte ratio; MLR – monocyte / lymphocyte ratio; SII – systemic immune-inflammation index; p value < 0.05

presents the cut-off values, AUC values for sensitivity and specificity, positive likelihood ratio, and negative likelihood ratio ratios. In the ROC comparative analysis applied to compare AUC values between the analyzed parameters, NEUTs were found to be more effective than monocytes in predicting miscarriage (p: 0.034). There was no statistically significant relationship when comparing the other parameters

Table 3. Correlation of AUC values between parameters analyzed by ROC

Table 3	SII	WBC	PLT	MONO	NEUT	NLR	MLR
SII		0.855	0.075	0.181	0.625	0.631	0.164
WBC	0.855		0.161	0.072	0.181	0.929	0.318
PLT	0.075	0.161		0.911	0.070	0.275	0.749
MONO	0.181	0.072	0.911		0.034	0.289	0.729
NEUT	0.625	0.181	0.070	0.034		0.423	0.121
NLR	0.631	0.929	0.275	0.289	0.423		0.205
MLR	0.164	0.318	0.749	0.729	0.121	0.205	

Abbreviations; AUC – area under the curve; WBC – white blood cells; PLT – platelet; MONO – monocyte; NEUT – neutrophil; NLR – neutrophil / lymphocyte ratio; MLR – monocyte / lymphocyte ratio; SII – systemic immune-inflammation index

A cut-off value of ≤692 in the ROC analysis — performed to investigate the effect of the SII value in predicting pregnancy outcomes — produced a sensitivity of 31.8% and a specificity of 83.3%. The AUC for the SII was 0.594 (95% CI: 55.8 to 63, p < 0.001)

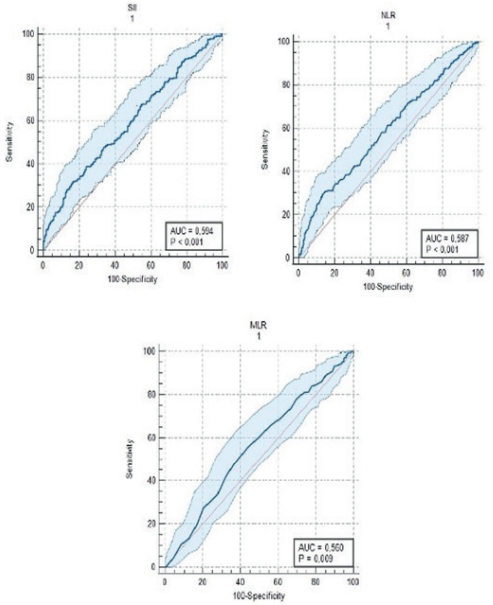

Figure 2. ROC analysis was performed to investigate the effect of SII (Fig.2a), NLR (Fig.2b), and MLR (Fig.2c) value in predicting the outcome of TM; SII – systemic immune-inflammation index; NLR — neutrophils-lymphocytes ratio; MLR — monocytes-lymphocytes ratio

The AUC for NLR was found to be 0.587 (p<0.001) in miscarriage (Figure 2). The sensitivity and specificity of the NLR were determined to be 30.9% and 85.4%, respectively, at a threshold NLR score of ≤2.53 for miscarriage. The AUC for MLR was found to be 0.560 (p = 0.008) in miscarriage (Fig. 2c). The sensitivity and specificity of the MLR were determined to be 55.6% and 55.9%, respectively, at a threshold MLR score of ≤0.21 for miscarriage.

The AUC for WBC was 0.589 (p < 0.001) in TM.

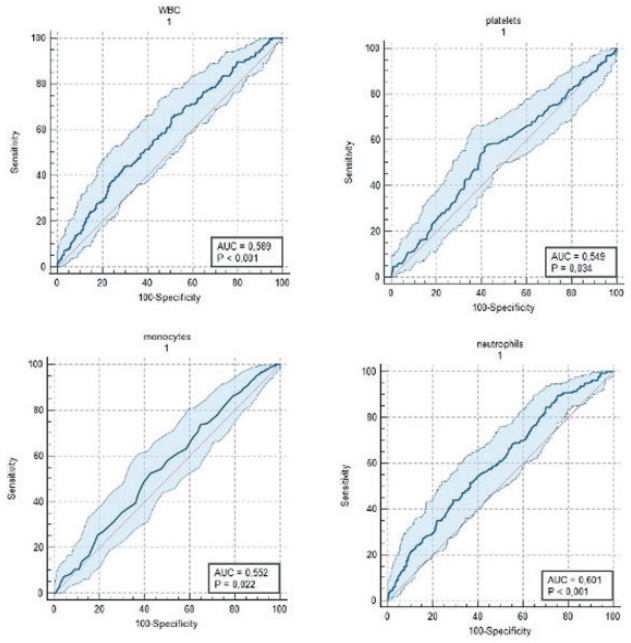

Figure 3. ROC analysis was performed to investigate the effect of WBC (Fig.3a), PLT (Fig.3b), MONO (Fig.3c), and NEUT (Fig.3d) value in predicting the outcome of TM; WBC – white blood cells; PLT— platelet; MONO — monocyte; NEUT – neutrophil

The sensitivity and specificity of the WBC were determined to be 65.5% and 49.1%, respectively, at a threshold WBC value of ≤9.42. Values >9.42 were significantly related to having a childbirth. The AUC for PLTs was found to be 0.549 (p = 0.034) in miscarriage (Figure 3). The sensitivity and specificity of the PLTs were determined to be 56.9% and 58.7%, respectively, at a threshold PLT value of ≤263 for miscarriage. The AUC for MONOs was found to be 0.552 (p = 0.022) (Figure 3). The sensitivity and specificity of the MONOs were found to be 52.6% and 57.4%, respectively, at a threshold MONO value of ≤0.4 in miscarriage. The AUC for NEUTs was found to be 0.601 (p<0.001) (Figure 3). The sensitivity and specificity of the NEUTs were found to be 43.9% and 70.9%, respectively, at a threshold NEUT value of ≤5.71 in miscarriage.

DISCUSSION

In the present study, we investigated the alteration of SII and other inflammatory markers in TM and their prognostic value in predicting pregnancy outcomes. According to our results, women whose pregnancy ended as a miscarriage had significantly lower SII levels in blood samples than women whose pregnancy ended as a healthy childbirth. In addition, logistic regression analysis clearly showed that decreased SII level is an independent risk factor for the development of spontaneous miscarriage at TM.

First-trimester hemorrhage is the most common complication in obstetrics and gynecology (16). This complication in early pregnancy is associated with various adverse pregnancy outcomes, such as incomplete/complete miscarriage, preterm delivery, premature preterm rupture of membranes (pPROM), placental abnormalities, FGR, etc (17). Recent studies have shown that approximately 13.7% to 50% of these first-trimester hemorrhages result in miscarriage (10,18). In our study, 32.7% of the TM population resulted in miscarriage.

Several factors, such as previous miscarriage, systemic diseases of the mother, such as diabetes mellitus and thyroid dysfunction, infertility treatments, maternal and paternal genetic defects, and older age of both mother and father, are risk factors for spontaneous miscarriage (5-9). However, regardless of these etiologic factors, first-trimester hemorrhage is an early indicator of placental dysfunction and progression to miscarriage in some cases of TM (10). Previous studies have shown that oxidative stress and systemic inflammation play a critical role in placental dysfunction and thus miscarriage (19). In recent years, there have been many studies on inflammatory markers to predict pregnancy outcomes (3,10,13,17,19). Although these studies endeavor to make predictions based on alterations in inflammatory markers throughout the course of pregnancy, it is important to consider that certain inflammatory markers, such as WBCs, tend to increase during this period (20). Additionally, a reduction in the ratio of granulocytes and T helper (Th)-1 LYMs, as well as a reduction in the ratio of Th-2 LYMs and MONOs, has been observed under typical conditions of normal pregnancy (20). In addition, increasing the number and activity of macrophages and monocytes plays an important role in placental development. Macrophages and monocytes promote extravillous trophoblast invasion, spiral artery remodeling, and parturition (20). Thus, these decreases and increases in inflammatory markers may result in different predictive thresholds for outcomes in pregnancy.

Inflammatory markers have gained attention in recent years, and the search continues for cost-effective, widely available, easily applicable, and interpretable biomarkers that can more accurately predict pregnancy outcomes. It is widely acknowledged that the most substantial alterations that occur during pregnancy are those that affect the immune system. Therefore, suppression of inflammatory processes is crucial for the acceptance of semi-allogeneic embryos. The findings of the present study indicated that SII levels in the blood samples of women whose pregnancies ended in miscarriage were significantly lower than those of women whose pregnancies ended in healthy births. Furthermore, the investigation demonstrated that decreased SII levels are indicative of spontaneous miscarriage in TM, thus establishing this as an independent risk factor.

In a study by Ata et al, the PLR score was found to be associated with first-trimester miscarriage, whereas the NLR score was not (21). In our study, the PLR score was not statistically significant between groups, but a low NLR score was significantly associated with miscarriage in the first trimester. A study by Sert et al found a significant association between a high SII score and miscarriage; high NLR and PLR scores were also associated with miscarriage (22). Another study by Soysal et al, whose results were consistent with those of the previous miscarriage prediction study, concluded that SII, NLR, MLR, and PLR scores were significantly elevated in patients with TM and that these higher scores could be a marker for predicting miscarriage in an ongoing pregnancy (23). In contrast to these two studies, a low SII score was associated with miscarriage, and pregnancies with a high SII score also ended in delivery in our study. As already mentioned and as far as we know, at the beginning of all pregnancies a certain inflammatory process was necessary. If this process was insufficient, the pregnancy ended in miscarriage or was terminated before implantation or development of the placenta. Similarly, our results showed that high first-trimester SII, MLR, and NLR scores in maternal blood led to delivery.

Our study has some limitations, mainly due to its retrospective nature. Because we lacked some information in the analysis of the data (such as maternal height, body mass index, etc.) that could influence the results, the lack of a power calculation represents the inherent limitations of the present study. The major strength of this study is that it was conducted in a large tertiary referral hospital that uses the same algorithms for diagnosis, management, and follow-up. It is also one of the studies with the highest number of patients on this topic.

CONCLUSION

Elevated SII in maternal blood indicates an inflammatory process but results in delivery. Gynecologists should be cautious about SII values of ≤692/L (sensitivity of 31.8% and specificity of 83.3%) for miscarriage. In contrast to other studies, our results showed that the inflammatory process may change from pregnancy to pregnancy. The CBC should be tested in the first and third trimesters routinely (21-23). So, physicians can easily achieve SII with these tests and be more cautious about the risk of miscarriage. So, pregnant women at risk for miscarriage may be informed well and monitored closely. However, further randomized controlled trials are needed to confirm our findings.

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Disclosure:

Ethics approval: This study was approved by Etlik Zübeyde Hanım Women's Health Training and Research Hospital Ethics Committee (dated 17.06.2020 and numbered 2020/70). All authors and the study protocol respected the World Medical Association Declaration of Helsinki on the ethical conduct of studies involving human subjects.

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Consent to participate: All human subjects provided written informed consents with guarantees of confidentiality

The authors declare no conflict of interest.

The article has not been published elsewhere and has not been submitted for publication.

Authors' contributions

YAR: Project Development, Data Collection or Management, Data Analysis, Manuscript Writing/Editing

FBF: Project Development, Data Collection and Management, Data Analysis, Manuscript Writing/Editing

AA, STS: Project Development, Data Collection and Management, Manuscript Writing/Editing

SYE, SÖ: Data Management, Data Analysis, Manuscript Writing/Editing

SE, YEÜ: Supervision, Manuscript Writing/EditingAll authors read and approved the final manuscript.

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