

# Systemic immune-inflammation index in twin pregnancies compared to singleton pregnancies

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#### Abstract

**Objective:** To evaluate the systemic immune-inflammation index (SII) in twin pregnancies.

**Methods:** The retrospective study included 200 twin (dichorionic/ diamniotic and monochorionic/diamniotic) and 200 singleton pregnancies (control group). All pregnant women were in the first trimester (<14 weeks of gestation). The study and the control groups were compared in terms of demographic characteristics, laboratory test results, and SII values.

**Results:** The mean week of gestation was  $9.7\pm2$  in dichorionic diamniotic twin pregnancy group,  $10.4\pm2$  in monochorionic diamniotic twin pregnancy group and  $9.4\pm2$  for the control group (p=0.083). The lymphocyte value was lower in the dichorionic group and monochorionic group than in the control group (p=0.020 and p=0.020, respectively). The platelet-to-lymphocyte ratio (PLR) values were higher in the dichorionic group than in the control group (p=0.002). However, there was no statistical difference between the groups for neutrophil-to-lymphocyte ratio (NLR) and SII values (p>0.05).

**Conclusion:** Physiological inflammatory/immune reaction of early pregnancy may affect PLR values in twin pregnancies. We observed that chorionicity is considerable for these inflammatory indices, especially for dichorionic twin pregnancies. However, we could not detect a significant change in SII values in twin pregnancy.

**Keywords:** Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, twin pregnancy.

#### Özet: Tekil gebeliklere kıyasla ikiz gebeliklerde sistemik immün-enflamasyon indeksi

Amaç: İkiz gebeliklerde sistemik immün-enflamasyon indeksini (SII) değerlendirmek.

Yöntem: Retrospektif çalışmaya 200 ikiz (dikoryonik/diamniyotik ve monokoryonik/diamniyotik) ve 200 tekil gebelik (kontrol grubu) dahil edildi. Tüm gebeler birinci trimesterdeydi (<14. gebelik haftası). Çalışma ve kontrol grupları, demografik özellikler, laboratuvar test sonuçları ve SII değerleri yönünden karşılaştırıldı.

**Bulgular:** Ortalama gebelik haftası dikoryonik diamniyotik ikiz gebelik grubunda 9.7±2, monokoryonik diamniyotik ikiz gebelik grubunda 10.4±2 ve kontrol grubunda 9.4±2 (p=0.083) idi. Lenfosit değeri dikoryonik ve monokoryonik gruplarda kontrol grubundan daha düşüktü (sırasıyla p=0.020 ve p=0.020). Trombosit-lenfosit oranı (PLR) değerleri dikoryonik grupta kontrol grubundan daha yüksekti (p=0.002). Ancak nötrofil-lenfosit oranı (NLR) ve SII değerleri bakımından gruplar arasında istatistiksel bir fark yoktu (p>0.05).

**Sonuç:** Erken gebeliğin fizyolojik enflamatuvar/immün reaksiyonu, ikiz gebeliklerde PLR değerlerini etkileyebilir. Koryonisitenin bu enflamatuvar indeksler için, özellikle de dikoryonik ikiz gebelikler için dikkate değer olduğunu gözlemledik. Ancak ikiz gebelikte SII değerlerinde anlamlı bir değişiklik tespit edemedik.

Anahtar sözcükler: Nötrofil-lenfosit oranı, trombosit-lenfosit oranı, sistemik immün-enflamasyon indeksi, ikiz gebelik.

## Introduction

Twin pregnancies constitutes 2–4% of the total number of births.<sup>[1,2]</sup> Twin pregnancy rate has been increased in the last 30 years due to advanced maternal age and increased application of assisted reproductive techniques.<sup>[3]</sup> Compared to singleton pregnancies, twin pregnancies have an increased risk of obstetric complications such as miscarriage, premature birth, anemia, and gestational hypertension. Altered adaptation during twin pregnancy is a leading cause of these various complica-

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tions.<sup>[4]</sup> Immune and inflammatory changes during pregnancy adaptation in twin pregnancies were evaluated with systemic inflammatory markers such as the neutrophil-lymphocyte ratio (NLR) previously, and significant differences were found.<sup>[5,6]</sup> The systemic immune inflammation index (SII) is a new marker including peripheral lymphocyte, neutrophil, and blood platelet counts.<sup>[7]</sup> It has been used as a clinical marker to predict the prognosis of the obstetric complications and oncological diseases in various studies.<sup>[8–11]</sup> In this study, we aim to evaluate the SII in twin pregnancy.

### **Methods**

The study was conducted in Ankara City Hospital between May 1 and September 15, 2021. Approval for the study was obtained from Ankara City Hospital Ethics Committee with the decision number E2-21-131. The retrospective study included 200 twins (144 dichorionic/diamniotic and 56 monochorionic/diamniotic twin pregnancies) and 200 singleton pregnancies and their complete blood counts were evaluated. An inclusion criteria for the groups was having a viable embryo within the first 14 weeks of gestation (first trimester). The gestational age of the pregnancies was established with fetal crown-rump length by ultrasonographic examination. Chorionicity was assigned according to the number of placental masses and T or  $\lambda$ -signs for a single placental mass by ultrasonographic examination. Women with fetal chromosomal/structural abnormalities, maternal bleeding, maternal hematologic and systemic diseases, or smoking during pregnancy were excluded. Maternal age, parity, BMI (kg/m<sup>2</sup>), rate of previous miscarriage (%), maternal chronic disease (%),

 Table 1. Baseline data and characteristics of the groups.

rates of in vitro fertilization (IVF) pregnancies, gestational age at diagnosis (in weeks), maternal hemoglobin (Hb) (g/dl) count, leukocyte ( $10^{3}/\mu$ L) count, lymphocyte ( $10^{3}/\mu$ L) count, neutrophil ( $10^{3}/\mu$ L) count, platelet ( $10^{3}/\mu$ L) count, neutrophil-to-lymphocyte ratio (NLR) (neutrophil/lymphocyte), platelet-to-lymphocyte ratio (PLR), and SII (neutrophil × platelet /lymphocyte) values were compared between the groups.

Statistical analysis was enforced using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were given as mean ± standard deviation for numerical data with normal distribution or median and minimum-maximum values for numerical data which do not follow a normal distribution. The normality of the variables was tested with both Shapiro-Wilk and Kolmogorov-Smirnov tests. Oneway ANOVA analysis (and post hoc test to compare groups in case of significant difference was found with univariate ANOVA) was used for statistical analysis of three categorical groups. Comparison of variables were performed by Pearson chi-square test and Fisher's exact test for categorical variables. A p-value <0.05 were considered statistically significant.

# Results

The study included 200 twins (144 dichorionic/diamniotic and 56 monochorionic/diamniotic twin pregnancies) and 200 singleton pregnant women. There was no monochorionic/monoamniotic pregnant woman in the study. **Table 1** demonstrates study population demographics. The groups showed similar maternal baseline characteristics. The mean week of gestation was  $9.7\pm2$  in dichorionic diamniotic twin pregnancy group,  $10.4\pm2$  in

	Control group (n=200)	Dichorionic group (n=144)	Monochorionic group (n=56)	p-value
Maternal age	28.1±5.2	29.4±5.2	28.5±5.4	0.143
BMI (kg/m²)	26.2±5.2	27.0±4.9	27.3±5.4	0.244
IVF	24 (12%)	26 (18.1%)	9 (16.1%)	0.282
Nulliparity	48 (24%)	33 (22.9%)	15 (26.8%)	0.296
Previous miscarriage (≥1)	26 (13%)	25 (17.4%)	6 (10.7%)	0.374
Gestational age (week)	9.4±2	9.7±2	10.4±2	0.083
Maternal chronic disease	11 (5.5%)	8 (5.6%)	5 (8.9%)	0.609

Data given as mean ± standard deviation. BMI: body mass index; IVF: in vitro fertilization.

monochorionic diamniotic twin pregnancy group and 9.4±2 for the control group (p=0.083). In Table 2, laboratory test results and SII values were compared between singleton, dichorionic/diamniotic and monochorionic/diamniotic twin pregnancy groups. There was a significant difference between the groups for Hb, lymphocyte and PLR values (p=0.001, p=0.016 and p=0.007, respectively). Hb level in maternal blood were significantly lower in the both dichorionic and monochorionic groups than in the control group (p=0.002, p=0.004, respectively). The lymphocyte value was lower in the dichorionic and monochorionic groups than in the control group (p=0.020 and p=0.020, respectively). The platelet-to-lymphocyte ratio (PLR) values were higher in the dichorionic group than in the control group (p=0.002). However, there was no statistical difference between the groups for neutrophil-to-lymphocyte ratio (NLR) and SII values (p>0.05).

## Discussion

Twin pregnancy is represented as a high-risk pregnancy due to increased adverse pregnancy outcomes. We hypothesized that first trimester hyperimmune changes may occur in twin pregnancies compared to singletons and consistently we found significantly higher values of PLR in dichorionic diamniotic twin pregnancies than controls. However, there was no difference in all groups for SII values.

In pregnant women, local adaptation of the maternal immune system allows for successful coexistence between the mother and the fetus.<sup>[12]</sup> Cytotoxic adaptive immune responses are diminished, while regulatory adaptive immunity is enhanced.<sup>[13,14]</sup> The fetal membranes and placental trophoblasts are directly exposed to maternal blood and tissues. The number of fetuses is significantly correlated with the activity of trophoblasts.<sup>[15]</sup> The studies have reported that twin pregnancies produce more trophoblasts than singleton pregnancies during the first trimester.<sup>[6,16]</sup> The T helper 1 (Th1): T helper 2 (Th2) balance was compared between twin and singleton pregnancies in the first trimester.<sup>[6]</sup> The mean Th1:Th2 ratio in twin pregnancies was found to be significantly lower than in singleton pregnancies, associated with increased maternal serum hCG levels.<sup>[6]</sup>

There is a growing number of studies evaluating altered immunity and inflammation-related obstetric complications. The NLR and PLR values were reported to be sensitive early biomarkers of inflammatory response in obstetric conditions.<sup>[17-19]</sup> NLR was found significantly higher in patients with preeclampsia, hyperemesis gravidarum, and cholestasis of pregnancy that all related with hyperinflammation.<sup>[17-19]</sup> Sabre et al.<sup>[5]</sup> evaluated 29 twin and 29 singleton pregnancies in the first trimester. They found that NLR was significantly higher in twin pregnancies. However, they found no difference in PLR values between groups. Contrarily, we observed significantly higher PLR values in the dichorionic diamniotic twin pregnancies than singleton pregnancies. This may be related to the low lymphocyte levels in the twin pregnancy group. However, there was an increase in NLR and SII values in both dichorionic and

 Table 2. Comparison of laboratory test results and SII values between singleton pregnancy, dichorionic/diamniotic and monochorionic/diamniotic twin pregnancy groups.

	Control group (n=200)	Dichorionic group (n=144)	Monochorionic group (n=56)	p-value
Hb (g/dl)	12.6±1.1	12.2±1.2*	12.1±1.3 <sup>†</sup>	0.001
Leukocyte (10³/µL)	8.5±2.6	8.1±2.6	8.9±2.3	0.160
Neutrophil (10³/µL)	6.7±3.1	6.5±2.3	6.4±2.1	0.737
Lymphocyte (10 <sup>3</sup> /µL)	2.0±0.7	1.8±0.6*	1.7±0.4 <sup>+</sup>	0.016
Platelet (10 <sup>3</sup> /µL)	269.0±71.2	269.3±61.7	264.1±62.8	0.875
NLR	3.6±2.1	4.4±2.1	4.1±2.1	0.055
PLR	146.2±58.3	184.7±70.3*	156.9±48.5	0.007
SII (10 <sup>9</sup> /L)	955.95±53.5	1178.45±120.7	1057.19±474.6	0.052

Data given as mean  $\pm$  standard deviation. \*Statistically significant difference between dichorionic group and control group (p<0.05); <sup>†</sup>statistically significant difference between monochorionic group and control group (p<0.05). **Control:** singleton pregnancies; **Hb:** hemoglobin; **NLR:** neutrophil-to-lymphocyte ratio; **PLR:** platelet-to-lymphocyte ratio; **SII:** systemic immune inflammation index.

monochorionic twin pregnancies, but no statistically significant difference was observed compared to the control group. The SII is a new marker that incorporates lymphocyte, neutrophil, and platelet parameters known to be associated with inflammation.<sup>[7,8]</sup> For predicting oncological disease prognosis, SII was used in different studies.<sup>[7–9]</sup> The SII value was evaluated for prediction of adverse neonatal outcomes in preterm premature rupture of membranes (PPROM), and researchers found significantly increased SII values in the patients with PPROM.<sup>[10]</sup>

Monochorionic twin pregnancies have higher perinatal complication risks than dichorionic twin pregnancies.<sup>[20]</sup> Riyami et al.<sup>[21]</sup> observed that high perinatal morbidity and mortality rate is likely due to frequent twinto-twin transfusion syndrome, prematurity, fetal growth restriction, and intrauterine fetal death. It has been investigated that it may cause high adverse pregnancy outcomes due to the greater fetomaternal antigenic differences in monochorionic pregnancies. However, Savvidou et al.<sup>[22]</sup> evaluated 666 twin pregnancies, and they observed chorionicity does not affect the incidence of preeclampsia in twin pregnancies. In this study, we compared NRL, PLR, and SII data in monochorionic and dichorionic twin pregnancies, considering the high rate of adverse pregnancy outcomes in monochorionic pregnancies. On the contrary, we did not detect any significant difference between monochorionic and dichorionic pregnancies. However, dichorionic twin pregnancy group had a significantly increased PLR values compared to singleton pregnancies. Placental weight is higher in dichorionic twin pregnancies compared to monochorionic pregnancies.<sup>[23]</sup> Therefore, it could be assumed that markers associated with inflammation may contribute to the higher immunological load with placental mass in dichorionic pregnancies.<sup>[22]</sup>

# Conclusion

In conclusion, there was significantly higher PLR values in twin pregnancies compared to controls. In addition, we observed that chorionicity is considerable for these inflammatory indices, especially for dichorionic twin pregnancies. This is the first study to evaluate the SII values in twin pregnancies. Future studies are needed to evaluate the relationship between SII assessment and adverse pregnancy outcomes in twin pregnancies. Our study has strengths and weaknesses. It is the first study to evaluate the SII value in twin pregnancies. Using of an inexpensive and easy-to-apply method against underestimation is the strength of our study. The limitation of our study is the retrospective evaluation of the data and lack of long-term outcomes of the study group.

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