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Could the First Trimester Complete Blood Cell Indices Be Used to Predict Adverse Outcomes in Pregnant Women with Asthma?

Astımlı gebe kadınlarda birinci trimester tam kan sayımı indeksleri olumsuz sonuçları tahmin etmek için kullanılabilir mi?

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Abstract: The objective of this study was to investigate the efficacy of complete blood cell indices, specifically the neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune-response index (SIRI), in predicting composite adverse outcomes in pregnant women with asthma. This study employed a retrospective cohort design, enrolling 307 low-risk pregnant women and 97 pregnant women with asthma. The neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune-response index (SIRI) were compared between pregnant women with asthma and the low-risk pregnancy group in the first trimester. A significant difference was observed in the first trimester SII between pregnant women with asthma and the low-risk pregnancy group (p=0.034). The neutrophil-to-lymphocyte ratio (NLR) and systemic immune response index (SIRI) demonstrated no significant differences between the groups. Moreover, pregnant women with asthma had significantly higher eosinophil count values as expected. The first trimester white blood cell count (WBC) and platelet count (PLT) were found to be significantly higher in the asthma group (p=0.014 and p=0.031, respectively). In the asthma group, no significant difference was found between the composite adverse pregnancy outcomes due to SII, SIRI, and NLR. Pregnant women with asthma exhibited significantly elevated values for SII, WBC, PLT and eosinophils. In our study, we observed no association between groups in complete blood cell indices due to the composite adverse effects of pregnancy. Further studies with larger groups are required to evaluate the efficacy of complete blood cell indices in pregnant women with asthma.
Keywords: Asthma, pregnancy, complete blood cell indices, perinatology, immune system

Özet: Bu çalışmanın amacı, astımlı gebelerde tam kan sayımı indekslerinin, özellikle nötrofil-lenfosit oranı (NLR), sistemik immün-inflamasyon indeksi (SII) ve sistemik immün-yanıt indeksinin (SIRI) bileşik olumsuz sonuçları öngörmedeki etkinliğini araştırmaktır. Bu çalışmada retrospektif bir kohort tasarımı kullanılmış ve 307 düşük riskli gebe ile 97 astımlı gebe çalışmaya dahil edilmiştir. Nötrofil-lenfosit oranı (NLR), sistemik immün-inflamasyon indeksi (SII) ve sistemik immün-yanıt indeksi (SIRI) ilk trimesterde astımlı gebeler ile düşük riskli gebelik grubu arasında karşılaştırıldı. Astımlı gebeler ile düşük riskli gebelik grubu arasında ilk trimester SII açısından anlamlı bir fark gözlendi (p=0.034). Nötrofil-lenfosit oranı (NLR) ve sistemik inflamasyon yanıt indeksi (SIRI) gruplar arasında anlamlı farklılık göstermedi. Ayrıca, astımlı gebelerde eozinofil sayısı beklendiği gibi anlamlı derecede yüksekti. İlk trimester beyaz küre sayısı (WBC) ve trombosit sayısı (PLT) astım grubunda anlamlı olarak daha yüksek bulunmuştur (sırasıyla p=0,014 ve p=0,031). Astım grubunda, SII, SIRI ve NLR'ye bağlı bileşik olumsuz gebelik sonuçları arasında anlamlı bir fark bulunmamıştır. Astımlı gebelerde SII, WBC, PLT ve eozinofil değerleri anlamlı derecede yüksek bulunmuştur. Çalışmamızda, gebeliğin bileşik yan etkilerine bağlı olarak tam kan hücresi indekslerinde gruplar arasında bir ilişki gözlenmemiştir. Astımlı gebelerde tam kan hücresi indekslerinin etkinliğini değerlendirmek için daha büyük gruplarla yapılacak ileri çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Astım, gebelik, tam kan sayımı indeksleri, perinatoloji, immün sistem

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1. Introduction

Asthma is a chronic respiratory disease that affects approximately 300 million people worldwide. The disease and its symptoms cannot be attributed to a single environmental or genetic cause. Rather, the essential diagnosis is made based on three major characteristics: (i) reversible airway obstruction, (ii) inflammation of the airway, and (iii) increased airway response due to variable stimuli (1). Asthma is one of the most prevalent comorbidities among pregnant women, affecting between 3% to 6% of pregnant women worldwide (2). Pregnant women with asthma are at an increased risk of adverse outcomes of pregnancy, both for the mother and the fetus. (3)

It is a well-documented phenomenon that asthma control levels often change during pregnancy. It is commonly accepted that approximately one-third of asthma patients experience exacerbation during pregnancy, with the majority of these occurring during the middle of the pregnancy. Conversely, approximately one-third of patients experience improvement, with no significant changes observed in the remaining one-third. However, a recent multicase-control study has demonstrated that the percentage of asthma cases that worsen during pregnancy is 18.8%, a figure that is lower than previous estimates. Furthermore, the study has indicated that the severity of the disease is significantly associated with the likelihood of asthma worsening during pregnancy (4). It is of paramount importance to treat asthma and to reduce the incidence of exacerbations during pregnancy, as this has a significant impact on the outcome of pregnancy. (5)

The complete blood count (CBC) is a commonly employed and readily accessible diagnostic tool. Its indices may indicate the presence of inflammation, tissue repair, cytokine secretion, and cell regeneration processes. (6) The three complete blood cell indices, namely the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the systemic immune-response index (SIRI), have been employed in clinical practice in recent years. (7) It is possible that these indexes may indicate an excessive inflammatory response within the human body.

A recent study has demonstrated that in individuals with asthma, elevated levels of SII and SIRI are associated with an increased prevalence of stroke. This association was particularly pronounced in individuals with coexisting obesity and hyperlipidemia. SII and SIRI are relatively stable novel inflammatory markers in the asthmatic population. SIRI demonstrates superior predictive value for stroke prevalence compared to SII (8).

The objective of this study was to assess the predictive value of NLR, SII, and SIRI in identifying composite adverse outcomes in pregnant women with asthma.

2. Materials and Methods

This retrospective case-control study was conducted at Ankara Bilkent City Hospital's perinatology clinic between 2020 and March 2023. All pregnant women with asthma who provided written informed consent to participate in the study were included. The demographic features, clinical characteristics, laboratory results, and complete blood cell indices were compared to a gestational age-matched control group who were followed up in the perinatology clinic during the study period. The study protocol was approved by the institutional ethics committee, which assigned reference number E2-23-4338.

The diagnosis of asthma was made in accordance with the GINA guidelines.(9) Asthma severity is classified according to the parameters defined by the National Asthma Education and Prevention Program Working Group on Asthma and Pregnancy. These parameters define four categories: mild, moderate, moderate with additional therapy, and severe. At the time of the initial blood sample collection during the first trimester, all patients were asymptomatic for SARS-CoV-2, or SARS-CoV-2 PCR results were negative. Moreover, cases with severe asthma were excluded from the study as the severity of the disease has significant impact on the complete blood count parameters and adverse pregnancy outcomes.

A composite adverse outcome was defined as the presence of at least one of the following pregnancy complications: preterm delivery, gestational hypertension, intrauterine fetal demise, fetal growth restriction, and oligohydramnios.

A comparison was conducted between the study and control groups regarding maternal age, gravidity, parity, live births, first-trimester complete blood cell parameters, neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune response index (SIRI). The following formulae were employed to calculate SII and SIRI:

SII = (platelet count x neutrophil count)/lymphocyte count

SIRI = (neutrophil count x monocyte count)/lymphocyte count

All blood samples were collected between 8 and 14 weeks of gestation during the patient's first admission to the hospital. Neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic immune response index (SIRI) were calculated based on first-trimester complete blood cell results. Additionally, the asthma group was divided into subgroups based on adverse pregnancy outcomes, which were then compared between the subgroups.

All patients with asthma were managed by a multidisciplinary team, comprising a pulmonary diseases specialist and a perinatologist.

All statistical analyses were performed by SPSS 22 (IBM Statistics, Chicago, USA). As the data were found to be normally distributed according to Shapiro Wilk Test, mean and standard deviation values were used to present continuous variables, and the student t-test was used to compare mean values between the groups. Categorical variables were presented as numbers and percentages. A chi-square test was performed to compare categorical values. A p-value <0.05 was considered statistically significant.

3. Results

A total of 92 pregnant women with asthma were compared to a gestational age-matched low-risk control group of 307 pregnant women. Table 1 presents a comparison of the demographic features, laboratory results, and complete blood cell indices between the study and control groups. Statistically significant higher values were observed for maternal age, white blood cell count, platelet count, eosinophils and SII in the asthma group compared to the low-risk group.

Table 1. Comparison of demographic features, and ultrasonographic measurements between the groups

	Control (n=307)	Asthma (n=92)	P
Maternal age (years)	28 (7)	30 (10)	**<0.001**
Gravidity	2 (2)	2 (2)	0.25
Parity	1 (2)	1 (2)	0.082
Wbc	9.04 (2.74)	9.69 (3.55)	**0.014**
Neutrophile	6.51 (2.35)	6.83 (2.92)	0.031
Lymphocyte	1.78 64)	1.79 (0.7)	0.64
Eosinophils	0.08 (0.1)	0.15 (0.13)	**<0.001**
Hgb	12.2 (1.8)	11.8 (1.5)	0.11
Hct	36.5 (5.7)	36 (3.6)	0.28
Plt	249 (89)	267 (131)	**0.031**
NLR	3.63 (1.89)	3.56 (2.1)	0.57
SII	904 (577)	1018 (682)	**0.034**
SIRI	1.6 (1.05)	1.71 (1.33)	0.086

Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell, Plt: platelet, NLR: neutrophil to lymphocyte ratio, SIRI: Systemic immune response index, SII: Systemic immune-inflammation index

In the asthma group, 35 (38%) of the pregnant women had a composite adverse outcome in their pregnancy. A total of 20 cases (21%) of preterm birth, 18 cases (19%) of intrauterine growth restriction, 6 cases of preeclampsia and 23 cases (25%) of low-birth-weight newborns were recorded. Additionally, 13 cases presented with oligohydramnios and one case resulted in intrauterine fetal demise. A comparison of demographic features, clinical characteristics, laboratory values, and complete blood cell indices between asthmatic patients with and without composite adverse outcome is presented in Table 2. It was observed that the composite outcome group exhibited higher numerical values with respect to complete blood count indexes. Nevertheless, despite the numerical higher values, no statistically significant difference was identified between the two groups. Conversely, the gestational age at birth, birth weight and 1st minute APGAR scores were markedly elevated in the asthmatic cohort that had not experienced a composite adverse outcome.

Table 2. Comparison of complete blood cell indices in pregnant women with asthma according to the presence or absence of composite adverse outcome

	Asthma without composite adverse outcome (n=57)	Asthma with composite adverse outcome (n=35)	p
Maternal age (years)	28.9±4.5	29.1±4.6	0.71
Gravidity	2±1.3	2±1.2	0.87
Parity	0.6±0.8	0.7±0.7	0.43
WBC	9.8±2.9	8.7±2.6	0.16
Neutrophil	9.21±2.83	7.66±4.34	0.23
Lymphocyte	1.53±0.31	1.74±0.51	0.2
Eosinophils	0.13± 0.15	0.16± 0.14	0.11
Hgb	11.7±2.3	12±1.9	0.6
Hct	35.3±3.2	36.2±3.9	0.43
Platelet	267±78	255±74	0.093
SII	1007 ±1053	1049 ±817	0.41
SIRI	1.63 ±1.41	1.77 ±1.37	0.32
NLR	3.44 ±2.43	3.66 ±1.73	0.27
Week of birth	37.3±2.3	38.8±1.1	**0.016**
Birth weight	2790±614	3244±402	**0.021**
APGAR 1st min	7.73±0.63	7.59±0.32	**0.043**
APGAR 5th min	8.87±0.44	8.71±0.5	0.17

Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell, Pct: plateletcrit, NLR: neutrophil to lymphocyte ratio, SIRI: Systemic immune response index, SII: Systemic immune-inflammation index

4. Discussion

The development of asthma is significantly influenced by inflammatory processes. Asthma is a chronic inflammatory disease that affects the number and mechanism of eosinophils, neutrophils, lymphocytes, and macrophages and their components.(10). In recent years eosinophils were the essential marker for asthma in complete blood cell count (CBC) studies(11). Meanwhile more recent studies focus on complete blood cell indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune response index (SIRI), and systemic immune-inflammation index (SII) etc. These CBC associated inflammatory biomarkers have been used to assess disease severity, exacerbations and predict morbidity and mortality(12).

Asthma is most common comorbidity in pregnancy. Approximately 4-8% of pregnant women are affected by this disease(13). In addition to the effect of maternal asthma on pregnancy outcomes, pregnancy may affect the course of asthma. The severity of asthma may improve, worsen, or remain unchanged during pregnancy; the mechanisms underlying changes in the severity of asthma during pregnancy remain undefined. Acute exacerbations have been observed in almost half of the patients and are a major problem during pregnancy. This leads the patients seek for medical assistance. Asthma in pregnancy also have a higher obstetric adverse outcome rate such as preterm delivery, gestational hypertension, gestational diabetes and low birth weight(14).

Complete blood cell indices show their clinical importance in various fields of medicine(15). Despite the numerous positive findings that have been obtained in the clinical application of complete blood cell indices, it is still unclear what role they play in the development and prognosis of diseases (16). It is still non-specific and heterogeneous in each disease. Nevertheless, studies to understand the total blood cell count in specific patient groups are necessary to obtain more meaningful results.

The association between asthma and adverse pregnancy outcomes has been known for decades, and there are numerous studies that have investigated this. Because of the oxygen requirements of the fetus, maternal oxygen levels are critical for the fetal oxygenation. This is a serious problem in acute exacerbations in pregnant women with asthma(17). Asthma is known to be associated with preeclampsia(18,19), placental abruption, placenta previa(20) and obstetric hemorrhage. A large cohort study from Canada of more than 15,000 women with asthma found an increased risk of spontaneous abortion (21).

In a single center retrospective cohort study, more than 2000 pregnant women with asthma were compared with more than 8000 randomly selected pregnant women. Maternal asthma has been found significantly associated with several composite adverse outcomes, including preterm birth, low-weight-birth infants whom small for their gestational

age, cesarean delivery and gestational hypertension (14).

A retrospective cohort study was conducted using the Health Care Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) database. The study population comprised 7,772,999 pregnant women, of whom 223,236 (2.9%) had asthma between 2003 and 2011. In the present study, the authors reported the discovery of statistically significant associations between composite adverse outcomes and maternal asthma (22).

A retrospective cohort study of pregnant women with asthma was conducted in a single center between 2009 and 2018. One of the findings of this study was that oligohydramnios rates were higher in moderate and severe asthma groups compared to the mild asthma group ($p<0.001$) (23). The authors claimed that they expected oligohydramnios and other composite adverse outcomes to include inadequate placental perfusion intrauterine growth restriction, gestational hypertension, and preeclampsia. This is a consequence of inadequate oxygenation of the placental vascular tree due to maternal asthmatic exacerbations. This situation might be correlated with asthma severity, number of exacerbations, type of medication, smoking status, asthma-related hospitalizations and air pollution (24).

A study found that a high blood eosinophil count was a risk factor for increased asthma exacerbations or hospital admissions in people with uncontrolled asthma. Furthermore, a high blood eosinophil count was identified as an independent risk factor for two or more asthma exacerbations, as well as any asthma emergency department visit or hospitalization (25). As anticipated, eosinophil counts were elevated in the asthma group in our study. However, no significant difference was observed in asthmatic pregnant women with and without composite adverse outcome. It is hypothesized that this discrepancy may be attributed to the fact that the asthma group encompasses patients with mild and moderate asthma.

In recent years, our knowledge of the role of complete blood cell indices has improved, and new indices such as SII and SIRI have entered the field. In a recent retrospective cohort study including a total of 48,305 participants found that the prevalence of asthma was found to be positively associated with these complete blood cell indices: NLR, PLR, MLR, SIRI and SII (12). Also, in this study gradient of these complete blood cell indices were associated with a higher percentile risk of mortality.

Considering the autoimmune and inflammatory background of the asthma, pregnant women have potential to be negatively affected by disease specific complications and relatively low oxygen levels. Moreover, physiologic changes observed during pregnancy may affect the prognosis of asthma. As complete blood cell indices reflect excessive inflammatory processes in the human body, the authors of the present manuscript aimed to investigate their possible role in the prediction of composite adverse outcomes in pregnant women with asthma. Furthermore, the severity of asthma was found to be closely associated with adverse outcomes in pregnant population. Thus, complete blood cell indices may be useful as they may represent the degree of inflammation in the maternal blood.

The asthmatic group exhibited significantly elevated white blood cell (WBC), platelet, eosinophil, and systemic immune index (SII) levels compared to the control group. No significant difference was observed in SIRI and NLR values between the two groups. Among asthmatic patients, there was no significant difference between the groups with and without composite adverse outcomes for NLR, SII, and SIRI. The limited number of patients in the asthma group and the exclusion of severe cases may be contributing factors.

5. Conclusion

This study's most notable strength was its incorporation of innovative indices, the inclusion of a substantial number of study parameters, and the incorporation of initial acceptance parameters. The principal limitation of this study was that it was conducted at a single center and included a relatively small number of participants. As a result, the severity of asthma in the patients included in the study was not sufficiently varied. In conclusion, further multicenter studies with larger patient populations are required to ascertain the efficacy of SII, SIRI, and NLR in predicting composite adverse outcomes in pregnant women with asthma.

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