

Role of first trimester inflammatory markers in predicting adverse obstetric and neonatal outcomes in maternal obesity

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ABSTRACT

Aims: To compare first trimester serum inflammatory markers in obese pregnant women with healthy pregnant women and to investigate the predictive value of these markers for pregnancy and neonatal outcomes

Methods: This prospective observational study included 46 pregnant women with maternal obesity and 60 healthy pregnant women without obesity. The demographic characteristics, obstetric and neonatal outcomes of the participants were evaluated, and the neutrophil-lymphocyte ratio (NLR), systemic inflammation index (SII: $\text{NLR} \times \text{platelet}$), systemic inflammation response index (SIRI: $\text{NLR} \times \text{monocyte}$), aggregate index of systemic inflammation (AISI: $\text{NLR} \times \text{platelet count} \times \text{monocyte}$), and PLR (platelet-lymphocyte ratio) were calculated. To evaluate the predictive value for neonatal intensive care unit (NICU) admission and adverse obstetric outcomes, receiver operating characteristic curves were generated and the area under the curve values were calculated.

Results: The demographic characteristics of both groups were similar. In the study group, adverse obstetric outcomes, and NICU requirement were increased. In the maternal obese group, inflammatory markers such as SII, SIRI, AISI, and NLR were significantly elevated. PLR was also increased in the study group. In ROC analysis, it was found that the levels of inflammatory markers to predict adverse obstetric and neonatal outcomes in obese pregnant women were statistically significant.

Conclusion: SII, SIRI, AISI, PLR, and NLR may be helpful in predicting neonatal and obstetric outcomes in maternal obesity.

Keywords: Obesity, pregnancy, systemic inflammation index, aggregate index of systemic inflammation

INTRODUCTION

Obesity continues to be a prevalent health problem worldwide. According to data from the World Health Organization, one in eight people live with obesity.¹ Obesity, particularly observed in women of reproductive age, leads to short- and long-term adverse obstetric and neonatal outcomes.² The inappropriate environment caused by the metabolic syndrome accompanying obesity-including hyperinsulinemia, chronic inflammation, increased oxidative stress, endothelial dysfunction, and vascular involvement-along with placental abnormalities, increases morbidity and mortality in both mothers and offspring. In obese mothers, increases may be seen in preeclampsia, diabetes, fetal distress, pregnancy loss, and the need for neonatal intensive care.³⁻⁵

In recent years, systemic inflammatory markers, which are indicators of inflammation and can be easily calculated from a complete blood count, have been shown to provide insight into disease prognosis during inflammatory processes. In a systemic inflammatory process, an increase in neutrophil count and a decrease in lymphocyte count were first defined as the neutrophil-to-lymphocyte ratio (NLR) in 2001 and

used as a prognostic value.⁶ In previous studies, with the addition of monocyte and platelet counts to neutrophil and lymphocyte counts, the Systemic Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Systemic Inflammation Aggregate Index (AISI) were developed. These inflammatory indices have been used in the course and prognostication of many diseases, including heart disease, cancer, and chronic illnesses.^{7,8}

Obesity has also become a serious health problem in pregnant women and creates a hyperinflammatory environment in both the mother and fetus. In this study, we aimed to compare first trimester serum inflammatory markers in obese pregnant women with those in healthy pregnant women and to investigate the predictive value of these markers for pregnancy and neonatal outcomes.

METHODS

This study is a prospective observational study, and ethical approval was obtained from the Ankara Bilkent City Hospital

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Ethics Committee (Date: 13.11.2024, Decision No: TABED 2-24-642). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written and oral informed consent was obtained from all participants. A total of 106 pregnant women, aged between 18 and 45 years, whose pregnancies were followed and deliveries occurred at the hospital between the years 2024-2025, were included in the study. The obese group consisted of 46 pregnant women with a body-mass index (BMI) of 30 kg/m² and above, who voluntarily agreed to participate in the study. The control group consisted of 60 pregnant women with a BMI below 30 kg/m², who had similar age and baseline characteristics to the study group and were randomly selected among those who wished to participate. Exclusion criteria included multiple pregnancy, chronic hypertension, pregestational diabetes, smoking, presence of any inflammatory disease, and a history of cancer.

Characteristics such as age, nulliparity, BMI, and neonatal outcomes of the participants were included in the study. According to the national guideline, the assessment of pregnancy up to the 14th gestational week is referred to as the first visit, during which a routine complete blood count is evaluated. From the participants' complete blood count results, the NLR, Systemic Inflammation Index (SII: NLR * platelet count), Systemic Inflammation Response Index (SIRI: NLR * monocyte count), systemic inflammation aggregate index (AISI: NLR * platelet count * monocyte count), PLR (platelet-to-lymphocyte ratio), and monocyte-to-lymphocyte ratio (MLR) were calculated.

Adverse obstetric outcomes included preterm labor, preterm premature rupture of membranes, hypertensive disorders of pregnancy, gestational diabetes, deep vein embolism, macrosomia (birth weight >4000 g), and fetal distress. Neonatal birth weight, APGAR score, and the need for neonatal intensive care unit (NICU) admission were recorded as separate outcomes. Inflammatory indices addressed in the study were analyzed to predict adverse obstetric history and NICU admission.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was tested using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Data were presented as median and interquartile range (IQR), number (n), and percentage (%) and were analyzed using the Mann-Whitney U test for non-parametric variables. A p-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were generated to assess the predictive value of NICU admission and adverse obstetric outcomes, and the area under the curve (AUC) values were calculated using standard methods. The data were presented as AUC ROC (95% CI). Optimal cut-off values for the inflammatory indices were calculated using the Youden index. In a similar study, estimation of sample size required at least 26 participants per group, assuming a 5% margin of error and 90% power.⁹

RESULTS

Table 1 presents the baseline characteristics of the participants. Maternal age, nulliparity, and the gestational week at which

the complete blood count was evaluated were similar between the two groups. In the obese group, 21 participants were nulliparous, compared with 25 in the healthy control group. The gestational weeks at delivery and birth weight were found to be significantly lower in the obese group compared to the healthy controls. While the APGAR scores were similar between the two groups, the obese group had higher rates of emergency cesarean section, adverse obstetric outcomes, and need for NICU admission. In the subgroup analysis according to parity and emergency cesarean section rates, the highest rate of emergency cesarean section was observed in the obese nulliparous group (n=11, 52.4%), whereas the lowest rates were found in the obese multiparous group (n=3, 12%) and the multiparous control group (n=5, 14.3%) (p=0.030).

Table 1. Baseline characteristics of participants

	Obese group (n=46)	Control group (n=60)	p-value
Maternal age (years)	30 (11)	27 (7)	0.053
Gestational age at scan (week)	9 (5)	9 (5.7)	0.411
Pregestasyonel BMI (kg/m ²)	33.5 (5.7)	26.6 (4.2)	<0.001
Nulliparity (n, %)	21 (45.6)	25 (41.6)	0.682
Gestational age at birth (week)	38 (3)	39 (2)	0.001
Birth weight (gram)	3210 (715)	3290 (495)	0.001
Emergency cesarean section (n, %)	14 (30.4)	15 (25)	0.006
APGAR score at 1 st minute	7 (1)	8 (1)	0.101
APGAR score at 5 th minute	9 (0)	9 (0)	0.208
NICU admission (n, %)	6 (13)	1 (0.01)	0.019
Adverse perinatal outcomes (n, %)	17 (36.9)	11 (18.3)	0.044

Note: Data given as median (interquartile range), number, percentile (%). p-values <0.05 were considered statistically significant.
BMI: Body-mass index, APGAR: Appearance, pulse, grimace, activity and respiration, NICU: Neonatal intensive care unit

In the obese group, six patients experienced fetal distress, two had hypertension, three had preterm labor, two had macrosomia, and one patient each had preterm premature rupture of membranes, uterine atony, deep vein thrombosis, and gestational diabetes. In the control group, fetal distress occurred in six patients, hypertension in two, and macrosomia in three. However, when each adverse obstetric outcome was analyzed separately, no statistically significant difference was observed between the groups.

Table 2 presents the first-trimester blood cell counts and inflammatory parameters for both groups. There was no difference in hemoglobin levels or lymphocyte counts between the obese and control groups. However, white blood cell count, neutrophil and monocyte counts, and platelet count-recognized as inflammatory markers-were significantly higher in the obese group (p=0.001; p<0.001; p=0.032; p=0.010, respectively). Additionally, the maternal obese group showed significantly higher levels of SII, SIRI, AISI, and NLR. The PLR was 138.8 (55.2) in the study group and 131 (48.7) in the control group (p=0.052). When participants were analyzed by parity, multiparous obese women (n=25) had significantly higher NLR (3.4 (1.7) vs. 2.8 (1); p=0.002), SIRI (1.4 (0.8) vs. 1.0 (0.7); p=0.001), AISI (353.3 (255.7) vs. 228.1 (165); p=0.001), and SII (840 (373.3) vs. 663.3 (230); p<0.001) compared to

multiparous non-obese women (n=35). In nulliparous obese women (n=21), SII and AISI were significantly higher than in nulliparous non-obese women (n=25) (SII: 918.9 vs. 632.2; p=0.003 and AISI: 431.6 vs. 269.4; p=0.008, respectively).

Table 2. Blood cell counts and inflammatory parameters in the first trimester of pregnancy in both groups			
	Obese group (n=46)	Control group (n=60)	p-value
Hemoglobin (g/dl)	12.5 (0.7)	12.5 (1.4)	0.182
Platelet (10 ⁹ /L)	254 (77)	237.5 (66.2)	0.010
WBC (10 ⁹ /L)	9.2 (3.9)	7.6 (2.8)	0.001
Neutrophil (10 ⁹ /L)	7 (2.6)	4.9 (1.9)	<0.001
Lymphocyte (10 ⁹ /L)	1.9 (0.7)	1.8 (0.7)	0.559
Monocyte (10 ⁹ /L)	0.5 (0.1)	0.3 (0.1)	0.032
Eosinophil (10 ⁹ /L)	0.1 (0.05)	0.06 (0.1)	0.465
SII	903.9 (622)	610.5 (228.8)	<0.001
SIRI	1.83 (0.8)	0.90 (0.6)	0.001
AISI	473.1 (343.6)	206.6 (176.6)	<0.001
NLR	3.5 (2.1)	2.5 (0.9)	0.002
MLR	0.25 (0.04)	0.19 (0.08)	0.059
PLR	138.8 (55.2)	131 (48.7)	0.052
Note: Data given as median (interquartile range), number, percentile (%). p-values <0.05 were considered statistically significant. WBC: White blood cell, SII: Systemic Inflammation Index, SIRI: Systemic Inflammatory Response Index, AISI: Aggregated Index of systemic inflammation, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to- lymphocyte ratio			

Tables 3 and 4 analyze the predictive value of systemic inflammatory indices for adverse obstetric outcomes and NICU admission (**Figure 1, 2**). For predicting adverse obstetric outcomes, the optimal cut-off values were 723.8 for SII and 282.2 for AISI, respectively (sensitivity 67.3%, specificity 67.9%, AUC 0.712; p=0.002 vs. sensitivity 64.3%, specificity 62.5%, AUC 0.681; p=0.007). For predicting NICU admission, the optimal cut-off values were 804.9 for SII and 348 for AISI, respectively (sensitivity 71.4%, specificity 71.2%, AUC 0.824; p=0.005 vs. sensitivity 71.4%, specificity 71.2%, AUC 0.732; p=0.044). However, when adverse obstetric outcomes were analyzed by subgroups, these parameters did not retain statistical significance.

Table 3. The ROC curve analysis for the performance of first trimester inflammatory markers in predicting adverse obstetric outcomes						
Variable	Cut-off	AUC	p-value	95% CI	Sensitivity	Specificity
NLR	2.8	0.549	0.468	0.441-0.687	50%	50%
SII	723.8	0.712	0.002	0.596-0.827	67.3%	67.9%
SIRI	1.21	0.638	0.039	0.510-0.767	60.7%	60.7%
AISI	282.2	0.681	0.007	0.559-0.803	64.3%	62.5%
PLR	138.6	0.517	0.789	0.386-0.648	52.9%	52.4%
Note: p-values <0.05 were considered statistically significant. ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic Inflammation Index, SIRI: Systemic Inflammatory Response Index, AISI: Aggregated Index of systemic inflammation, PLR: Platelet-to- lymphocyte ratio						

Table 4. The ROC curve analysis for the performance of first trimester inflammatory markers in predicting NICU admission						
Variable	Cut-off	AUC	p-value	95% CI	Sensitivity	Specificity
NLR	3.04	0.704	0.077	0.489-0.918	57.1%	61.6%
SII	804.9	0.824	0.005	0.707-0.941	71.4%	71.2%
SIRI	1.23	0.661	0.160	0.465-0.858	57.1%	56.2%
AISI	348	0.732	0.044	0.563-0.901	71.4%	71.2%
PLR	148	0.716	0.060	0.493-0.940	71.4%	67.1%
Note: p-values <0.05 were considered statistically significant. ROC: Receiver operating characteristic, NICU: Neonatal intensive care unit, AUC: Area under the curve, CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic Inflammation Index, SIRI: Systemic Inflammatory Response Index, AISI: Aggregated Index of systemic inflammation, PLR: Platelet-to- lymphocyte ratio						

DISCUSSION

To the best of our knowledge, this is the first study to investigate the relationship between serum inflammatory parameters and obstetric outcomes in maternal obesity. In obesity, increased visceral adipose tissue and elevated free fatty acids lead to a shift from an optimal intrauterine environment to a proinflammatory milieu due to elevated cytokines such as TNF- α , IL-1, and IL-6, as well as reactive oxygen species, ultimately resulting in chronic inflammation.¹⁰ Furthermore, maternal obesity can cause oxidative stress damage in the placenta, altering DNA methylation and mRNA expression, thereby affecting the fetus during intrauterine life.¹¹ One study reported that the chronic low-grade inflammatory environment and fetal malprogramming induced by obesity negatively affected neurodevelopment in offspring of obese mothers, showing disruptions in microglia and synaptic structures.¹² Similarly, in a murine model, maternal obesity was shown to cause fetal cardiac remodeling and dysfunction.¹³ Beyond fetal anomalies, obesity has also been associated with adverse obstetric outcomes. In obese pregnant women, similar to our study, the rate of primary cesarean section due to fetal distress has been found to be increased.¹⁴ Particularly in pregnancies with a BMI over 40 kg/m², the risk of fetal acidosis at birth is elevated.¹⁵ Consistent with these findings, a higher rate of adverse obstetric outcomes in the obese group was observed in our study. Although we did not find statistically significant differences among the subgroups of adverse obstetric outcomes in this study, we believe that this may be due to the limited number of participants. A meta-analysis has shown an association between high maternal BMI and macrosomia, preterm birth, and neonatal asphyxia.¹⁶ Another recent meta-analysis reported increased rates of gestational diabetes and hypertension with preeclampsia in obese women.¹⁷

In a 7-year population-based study including over 20,000 adult participants, obesity was found to be positively associated with systemic inflammatory parameters.¹⁸ Similarly, a recent large-scale study demonstrated a positive correlation between visceral adipose tissue and the SII in adults.¹⁹ Increased visceral adipose tissue in obese individuals may contribute to a pro-inflammatory environment through elevated adipokines and proinflammatory mediators. Comparable results have been observed in obese children, where NLR, SIRI, SII, and PLR were higher in obese children diagnosed with metabolic

syndrome compared to obese children without metabolic syndrome.²⁰

Systemic inflammatory parameters have been used to predict various maternal diseases, adverse pregnancy outcomes, and complications such as preeclampsia, fetal growth restriction, preterm premature rupture of membranes, and diabetes. In pregnancies diagnosed with gestational diabetes, elevated first-trimester SIRI and SII values have been reported.²¹ In another study, high SII and AISI levels were found to be statistically significant in predicting gestational diabetes; however, no significant association was observed with adverse obstetric outcomes or NICU admissions.²² In patients undergoing cervical cerclage due to cervical insufficiency, high SII and SIRI were associated with unsuccessful cerclage and poor neonatal outcomes.²³ Similarly, in our study, elevated SII and AISI were statistically significantly associated with adverse obstetric outcomes and NICU admission. Additionally, we found that although within normal limits, platelet counts were higher in the obese group compared to the healthy controls. Recent studies suggest that platelets (PLT) play a role not only in hemostasis but also in inflammation.^{24,25} Upon PLT activation, soluble inflammatory mediators are released, and the migration and activation of cells involved in inflammation, such as monocytes, leukocytes, and macrophages, are triggered. In a study conducted on adults, PLT counts and SII were higher in the obese group, while no statistically significant difference was found in PLR.²⁶ Another study in children with obesity reported elevated levels of neutrophils, PLT, and PLR.²⁷ In a large study involving nearly 3,000 children and adolescents, a significant positive correlation was found between BMI and both SII and SIRI.²⁸

The results of studies examining maternal diseases are consistent with studies on systemic inflammatory parameters and disease course and prognosis. In pregnant women with familial mediterranean fever (FMF), first-trimester NLR, SII, and SIRI levels were higher compared to healthy pregnant women, and these inflammatory markers were also elevated in FMF patients with perinatal complications compared to those without complications.²⁹ Similar findings have been reported in previous studies involving pregnant women with systemic lupus erythematosus, thrombophilia, and ulcerative colitis.^{9,30,31} An interesting study on systemic inflammatory parameters found that SIRI, SII, and NLR were elevated in cesarean scar pregnancies, and high SII levels were significantly associated with predicting scar pregnancy in women with a history of cesarean delivery.³²

Limitations

While our study is valuable in that it includes first-trimester serum inflammatory parameters and evaluates pre-pregnancy BMI and birth outcomes, its limitations include the relatively small sample size and the lack of subgroup analysis for adverse obstetric outcomes. Further large-scale studies on this topic are needed to obtain more definitive results.

CONCLUSION

SII, SIRI, AISI, PLR, and NLR may be helpful in predicting neonatal and obstetric outcomes in maternal obesity.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Bilkent City Hospital Ethics Committee (Date: 13.11.2024, Decision No: TABED 2-24-642).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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