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Changes in the Maternal Serum Inflammatory Parameters of Pregnant Women with Epilepsy

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Abstract

Objective: This study investigated the third-trimester maternal serum inflammatory status of pregnant women with epilepsy (PWWE).

Methods: One hundred-two PWWE and 102 healthy pregnant women were included in the study. Data were retrospectively collected from hospital records between May 2020 and 2023. The results of monocyte, neutrophil, lymphocyte, platelet counts, neutrophil-to-lymphocyte ratio (NLR), and serum C-reactive protein (CRP) levels were recorded. The systemic immune inflammation index (SII) and systemic inflammation response index (SIRI) were calculated. The presence of seizures and receiving antiseizure medications during pregnancy were recorded.

Results: Gestational age at delivery and birth weights of neonates were significantly lower in the epilepsy group than in the control group ($p<0.001$). The median NLR was 4.79 (2.36-10.50) in the polytherapy group and 2.87 (2.40-4.05) in the drug-free group, and this value was found to be statistically higher in the polytherapy group ($p=0.025$). No statistical significance was observed for NLR, CRP, SII, and SIRI values between the epilepsy group and the control group ($p>0.05$).

Conclusion: This study revealed that maternal serum inflammatory parameters did not differ between PWWE and healthy pregnant women. Having epileptic seizures or being seizure-free during pregnancy did not alter the maternal serum inflammatory status. Prospective large population studies conducted in the postictal acute and interictal phases are needed to reveal the effect of seizures on the inflammatory process in PWWE.

Keywords: Epilepsy, inflammation, pregnancy

INTRODUCTION

Epilepsy affects almost 1% of the general population and is the most common neurological disorder in pregnancies. The use of multiple antiseizure medications (ASMs), the frequency and severity of epileptic seizures, and drug-resistant epilepsyirectly affect the risk status of pregnant women with epilepsy (PWWE).[1] At least 9 months of seizure-free time before pregnancy is associated with a high rate of remaining seizure-free during pregnancy.[2] The risk of mild preeclampsia during pregnancy is 1.8 times, the risk of gestational hypertension is 1.5 times, the risk of vaginal bleeding in late pregnancy is 1.9 times, and the risk of preterm delivery is 1.5 times increased in PWWE using ASMs compared with healthy pregnant population.[3]

Inflammation may contribute to seizures, and anti-inflammatory therapies may treat seizures.[4] Some ASMs, such as valproate and levetiracetam, have anti-inflammatory effects by reducing serum levels of the C-C motif ligand 2.[5] It has also been found that glucocorticoids are effective in pediatric drug-resistant seizures and reduce the frequency of seizures.[6]

The neutrophil-to-lymphocyte ratio (NLR) is a reliable, cheap, and easy-to-apply marker of the immune response. NLR is influenced by many medical conditions such as chronic diseases, stroke, diabetes, cancer, and stress. NLR helps distinguish severe diseases from milder one.[7] NLR has been found to be higher in the acute and subacute phases of seizures than in healthy people. Elevated NLR is accepted as

a biomarker of inflammation and epilepsy.[8] The systemic immune inflammation index (SII) and systemic inflammation response index (SIRI) are derived from inflammatory maternal blood count parameters, positively associated with systemic inflammation, and reflect local and systemic immune responses. SII and SIRI have been used to estimate the risk of ischemic stroke, cardiovascular diseases, and overall survival of patients with cervical cancer.[9,10]

We hypothesized that the inflammatory process in epilepsy may affect maternal serum blood parameters. We aimed to investigate whether there is an association between inflammatory parameters and the occurrence of seizures by evaluating maternal serum inflammatory parameters such as C-reactive protein (CRP), NLR, SII, and SIRI in PWWE.

METHODS

This study was designed as a retrospective case-control study. The study was conducted on 102 PWWE and 102 healthy pregnant women who attended Ankara City Hospital's antenatal and perinatology outpatient clinic. Pregnant women who were diagnosed with epilepsy and followed up routinely between May 2020 and 2023 were included in the study group. Randomly selected healthy pregnant women without any systemic disease were used as the control group. Taking any medication except for ASMs, smoking, having no systemic or pregnancy-related disease, and having multiple pregnancies were exclusion criteria. The data of the patients were retrospectively obtained from the hospital records. Ethical approval was obtained from the University of Health Sciences Turkey, Ankara Bilkent City Hospital Institutional Review Board (no: E2-23-4486, date: 12.07.2023) for this study.

Third-trimester maternal serum complete blood count results were recorded for all patients. The results of monocyte, neutrophil, and lymphocyte counts, platelet counts, NLR, and serum CRP levels were recorded. SIRI was calculated by the formula (SIRI=monocyte counts × neutrophil counts/lymphocyte counts) and the SII index was calculated by the formula (SII=peripheral platelet counts × neutrophil counts/lymphocyte counts. The presence of seizures and receiving ASMs during pregnancy were recorded. Maternal age, obstetric history, gestational age at birth, birth weight of neonates, and hospitalization information in the neonatal intensive care unit (NICU) were recorded.

Statistical Analysis

IBM Statistical Package for the Social Sciences version 25.0 software (IBM Corp. Armonk, NY, United States) was used for statistical analyzes. The variables were analyzed using the Kolmogorov-Smirnov test to determine whether they were normally distributed or not. Descriptive analyzes were performed using medians (minimum-maximum) for non-normally distributed variables and mean standard deviation for normally distributed variables. The Mann-Whitney U test was used to compare two independent non-normally distributed variables. The variables with a normal distribution were compared using a parametric test (Student's t-test). The chi-square test was used for categorical variables. The Kruskal-Wallis test was used to compare more than two non-normally distributed independent variables. A p value of 0.05 was considered to show statistically significant results.

MAIN POINTS

- Pregnant women with epilepsy (PWWE) under polytherapy had a higher neutrophil-to-lymphocyte rate than drug-free pregnant women with epilepsy PWWE.
- Having epileptic seizures or being seizure-free during pregnancy did not alter the maternal serum inflammatory status.
- Maternal serum inflammatory parameters were not different between PWWE and healthy pregnant women.

RESULTS

Obstetric and clinical features of the epilepsy and control groups are shown in Table 1. The mean age, number of gravidas, and abortus were similar between the groups. Gestational age at delivery and birth weights of neonates were significantly different between the groups (p<0.001). While the NICU hospitalization rate was 21.6% in the maternal epilepsy group, it was 2.9% in the control group. This result was statistically significant (p<0.001). No statistical significance was observed for NLR, CRP, SII, and SIRI values (p>0.05).

A comparison of serum inflammatory parameters according to the presence of seizures is shown in Table 2. PWWE were divided into two groups according to whether they had seizures during pregnancy or not. No seizure was observed during pregnancy in 54.9% of the patients, whereas 45.1% of the patients had one or more seizures during pregnancy. NLR, CRP, SII, and SIRI values were similar (p>0.05).

In Table 3, epilepsy patients were divided into subgroups as monotherapy, polytherapy, and drug-free during pregnancy. Eleven of 102 patients (10.78%) did not take any medication during pregnancy. Eighty-four of 102 (82.35%) were treated with monotherapy, with 50 (49.01%) receiving levetiracetam, 14 (13.72%) receiving carbamazepine, 14 (13.72%) receiving lamotrigine, 5 (4.90%) receiving valproate, 1 (0.98%) receiving

Table 1. Obstetrics and clinical features of epilepsy and control group

	Epilepsy group n=102	Control group n=102	p value
Age	28 (18-42)	27 (18-39)	0.599[a]
Gravida Primigravid/multigravid	39/63	39/63	1.0[b]
Abortus	0 (0-6)	0 (0-3)	0.206[a]
Gestational age at birth (weeks)	37.5±2.62	38.8±1.31	**<0.001**[c]
Birth weight (grams)	2971±616	3289±409	**<0.001**[c]
NICU administration Yes (%)/No (%)	22 (21.6%)/80 (78.4%)	3 (2.9%)/99 (97.1%)	**<0.001**[b]
NLR	3.30 (0.74-10.65)	3.59 (1.16-11.17)	0.831[a]
CRP	5.15 (0-150)	10 (0-40)	0.961[a]
SII	870 (323-3130)	905 (344-2535)	0.751[a]
SIRI	1.40 (0.34-8.63)	1.42 (0.35-4.97)	0.442[a]

[a]Mann-Whitney U test; results were presented as median (min-max).
[b]Chi-square test; results were presented as number (%).
[c]Student's t-test; results were presented as mean±standard deviation.
p<0.05 values were presented in bold.
NICU: Neonatal intensive care unit, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, min-max: Minimum-maximum

Table 2. Comparison of serum inflammatory parameters according to the presence of seizures

	Seizure free group n=56 (54.9%) Median (min-max)	Seizure group n=46 (45.1%) Median (min-max)	p value[a]
NLR	3.26 (0.74-7.86)	3.73 (1.35-10.65)	0.114
CRP (mg/L)	5.15 (0-100)	4.90 (0-150)	0.398
SII	874 (382-2114)	870 (323-3130)	0.431
SIRI	1.48 (0.34-4.17)	1.38 (0.43-8.63)	0.809

[a]Mann-Whitney U test; results were presented as median (min-max).
NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, min-max: Minimum-maximum

Table 3. Comparison of serum inflammatory parameters according to anti-seizure medication type

	Drug free group n=11 (10.8%) Median (min-max)	Monotherapy group n=84 (82.4%) Median (min-max)	Polytherapy group n=7 (6.9%) Median (min-max)	p value[a]
NLR	2.87 (2.40-4.05)*	3.30 (0.74-10.65)	4.79 (2.36-10.50)*	**0.025**
CRP	5.30 (0-20)	4.95 (0-150)	10 (0-20)	0.876
SII	717 (515-1766)	879 (323-3130)	1341 (698-2507)	0.100
SIRI	1.17 (0.67-3.0)	1.38 (0.34-8.63)	2.25 (1.32-8.01)	0.099

[a]Kruskal-Wallis test. p<0.05 values were presented in bold.
*The difference is statistically significant.
NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, min-max: Minimum-maximum

oxcarbazepine. An additional 7 (6.86%) patients were treated with polytherapy, including various combinations of levetiracetam, carbamazepine, lamotrigine, valproate, and lacosamide, to control the seizures during pregnancy. The NLR was 4.79 (2.36-10.50) higher in the polytherapy group than in the drug-free group 2.87 (2.40-4.05) and this difference was statistically significant (p=0.025). The other serum inflammatory parameters (CRP, SII, and SIRI) did not differ between the groups.

DISCUSSION

In PWWE, the risk of perinatal complications and hospitalization increases during the antenatal, intrapartum, and postpartum periods. However, most women have a safe and normal pregnancy and delivery process. In our study, we found that the birth weight of newborns in the PWWE group was lower, the rate of admission to the intensive care unit was higher, and the gestational age at birth was lower. These findings were consistent with those reported in the literature.[11] Having epileptic seizures or being seizure-free during pregnancy did not alter the maternal serum inflammatory status or vise versa. PWWE who were treated with polytherapy had a higher NLR rate than women not taking any ASMs during pregnancy.

Overall, the theory that inflammation contributes to seizures is not clearly identified and is supported only by experimental studies. Impaired regulation of inflammatory cells is a critical and initiating step in the development of epileptogenesis. However, the pathophysiology remains unclear. Peripheral inflammation may damage the blood-brain barrier and initiate or aggravate epileptogenesis in systemic diseases such as SLE or RA. Controlling inflammation and prophylaxis in these disorders may reduce the risk of developing epilepsy.[4,12] Aronica and Crino[13] noted that the levels of inflammatory mediator cytokines, such as IL-6 and IL-1 receptor antagonists, reversibly increased both in the cerebrospinal fluid and serum of chronic epilepsy patients within 24 h after a tonic-clonic seizure. A study suggested that daily generalized motor seizures in children result in elevated IL-6 levels, leading to increased CRP.[14] Another study on rats observed that blood CRP and proinflammatory cytokine levels of rats with chronic seizures decreased after omega-3 treatment.[15] Our study did not find any statistical difference in serum CRP levels between the maternal epilepsy and control groups. The type of medication and presence of seizures during pregnancy did not change the CRP levels.

A recent systematic review that investigated NLR in epilepsy stated that elevated NLR values in the acute or subacute phase can be a good biomarker of inflammation for epilepsy.[8] Similarly, Güneş and Büyükgöl[16] found increased NLR values and blood cell inflammatory indices in the acute phase of epileptic seizures. A study of 116 enrolled patients noted that NLR could be a predictor and correlated with the length of hospitalization and need for ICU admission in adults with status epilepticus.[17] However, studies have also reported opposing views in the literature.[18,19] Faruk Ozdemir et al.[18] did not find any correlation between NLR and the duration and frequency of epilepsy in adult patients undergoing epilepsy surgery. Morkavuk et al.[19] did not find any difference in pre-and post-seizure NLR values in epilepsy patients. None of these studies were conducted in an epileptic pregnant population. In our study, NLR values were similar in both the epilepsy and control groups. However, the NLR values in both pregnant groups in our database were higher in the epilepsy and control groups. For example, the NLR value was found to be 2:66±3:70 in the epilepsy group and 1:83±0:49 in the control group in one study, and the pre-seizure NLR value was found to be 1.81 (0.88-3.71) in the generalized onset epileptic seizure group, 2.16 (0.83-3.67) in the focal onset epileptic seizure group, and 1.51 (0.84-3.64) in the PNES group in another study.[8,19] On the other hand, the placenta functions as a transient endocrine organ, and pregnancy may cause increased cortisol levels.[20] Cortisol may be a major driver of NLR variations because increased levels of cortisol are known to increase the neutrophil count while simultaneously decreasing the lymphocyte

count.[17] Combining these data that increased cortisol in pregnancy may be the factor that the NLR value both in epilepsy and control pregnant women are high in our data compared with the nonpregnant population in the literature. Bai et al.[21] found that SII and NLR in three pregnant trimesters increased in healthy pregnant women, which supports our findings. However, NLR rates were found to be higher in PWWE who received polytherapy during their pregnancy than in those who did not use drugs. One study found that ASMs did not affect NLR levels in epilepsy patients in the literature, and to the best of our knowledge, there is no data about the effect of ASM on NLR in epilepsy patients.[8] Studies are needed to reveal whether ASMs affect NLR values in patients with epilepsy.

Study Limitations

The major limitation of this study, we randomly collected blood samples and did not take samples at the acute or subacute phase of the seizure. We retrospectively examined serum inflammatory parameters from hospital records, and only the results of third-trimester serum blood samples were evaluated. Another limitation was the lack of subgroup analysis according to the type of antiepileptic drug used. The small number of the ASM-free and polytherapy groups was also a limitation, and a large number is needed for a more accurate evaluation in future studies.

CONCLUSION

To the best of our knowledge, this is the first study to evaluate serum inflammatory parameters such as SII, SIRI, and NLR values in PWWE. This study revealed that maternal serum inflammatory parameters do not differ between PWWE and healthy pregnant women. In addition, we did not find any association between maternal serum inflammatory parameters and seizures during pregnancy. Prospective large population studies conducted in the postictal acute and interictal phases are needed to reveal the effect of seizures on the inflammatory process in PWWE.

Ethics

Ethics Committee Approval: This case-control study was approved by the University of Health Sciences Turkey, Ankara Bilkent City Hospital Institutional Review Board (no: E2-23-4486, date: 12.07.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.L.K., D.T.E., Ö.Ü., O.Ö., Ö.K., D.Ş., Concept: B.L.K., D.T.E., Ö.Ü., G.K., O.Ö., Ö.K., D.Ş., Design: B.L.K., D.T.E., Ö.Ü., G.K., O.Ö., Ö.K., D.Ş., Data Collection or Processing: B.L.K., D.T.E., Ö.Ü., O.Ö., Analysis or Interpretation: B.L.K., G.K., Ö.K., Literature Search: B.L.K., G.K., Ö.K., Writing: B.L.K., G.K., Ö.K., D.Ş.

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