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Role of Platelet Indices in Pregnant Women with Epilepsy

Duygu Tuğrul Ersak[1], Özgecan Üçyıldız[1], Muradiye Yıldırım[1], Onur Özkavak[1], Güray Koç[2], Atakan Tanacan[1], Özgür Kara[1], Dilek Şahin[1]

[1]University of Health Sciences Turkey, Ankara City Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey

[2]University of Health Sciences Turkey, Ankara City Hospital, Clinic of Neurology, Ankara, Turkey

Duygu Tuğrul Ersak MD

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Corresponding Author: Duygu Tuğrul Ersak MD, E-mail: dygtgrl@gmail.com

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Abstract

Objective: This study aimed to investigate the inflammatory platelet (Plt) indices; Plt/lymphocyte, Plt/monocyte ratio (PMR), and Plt/neutrophil ratio (PNR) in maternal epilepsy patients.

Methods: Patients diagnosed with maternal epilepsy in a tertiary center between 2019 and 2022 were included in this retrospective case-control study. Consecutive uncomplicated healthy pregnant women constituted the control group. Complete blood count (CBC) parameter results and Plt indices during the first trimester of pregnancy were recorded. Neonatal outcomes, seizure history of epilepsy patients during pregnancy, and antiepileptic drugs used were also recorded.

Results: One hundred thirteen pregnant epilepsy patients were included in this study. As a control group, 339 healthy pregnant women were included. While the Plt was $271x10^9$/L in the epilepsy group, it was $249x10^9$/L in the control group (p=0.029). PMR and PNR were significantly higher in the epilepsy group. Fifty of the epilepsy patients had seizures during pregnancy (44.2%). When compared, no significant difference was found between epilepsy patients with a seizure history or not, as to demographic features and CBC parameters during the 1st trimester of pregnancy (all p>0.05).

Conclusion: Pregnant women with epilepsy have low-grade inflammation during the first trimester. Inflammatory Plt indices may be used in combination with other parameters for the management of pregnancy. Further studies are required.

Keywords: Epilepsy, pregnancy, inflammation, platelet, complete blood parameter indices

INTRODUCTION

Epilepsy is the most common chronic neurological disease with an incidence of 0.3-0.7% in pregnant women.[1] Epilepsy was shown to be stable in almost more than half of the patients during pregnancy. However, in 25-30% of the patients, the frequency of epileptic seizures was shown to be increased, and the fetal-neonatal outcomes remain obscure.[2]

In animal models, inflammation has been shown to trigger epileptic activity.[3] The pathological examination of brain tissues of children with epilepsy operated due to intractable seizures was reported to have inflammatory changes.[4] Additionally, antiepileptic drugs such as steroids act as anti-inflammatory interactions.[3,5] Marchi et al.[6] evaluated the inflammatory pathways in seizure disorders, suggesting that inflammation plays a role in the etiology of epilepsy.

Inflammatory maternal blood count parameters that are easily accessible have been studied in the obstetric field to predict adverse outcomes.[7-9] Neutrophil lymphocyte ratio (NLR) and platelet (Plt) lymphocyte ratio (PLR) were assessed in patients with epilepsy. An increase in NLR was shown to be associated with epileptic seizures.[10] In a systematic review, patients with epilepsy in the acute phase of the disease had higher NLR values.[11] In contrast, in another study, no difference was observed in NLR and PLR levels in epilepsy patients compared with healthy controls.[12] Systemic inflammatory markers were evaluated in patients with brain pathologies. No statistical difference was seen between the temporal lobe epilepsy patients and the control group in terms of inflammatory markers. NLR and PLR values were found to be lower in the temporal lobe epilepsy patients than in the meningioma and glioma patients.[13] Epilepsy was shown to have chronic low-grade inflammation, not severe acute inflammation, suggesting stable levels of inflammatory markers.[14] The results in the literature are contradictory regarding inflammatory markers and epilepsy.[15] Therefore, in this study, we aimed to investigate the

inflammatory Plt indices; PLR, Plt/monocyte ratio (PMR), and Plt/neutrophil ratio (PNR) in maternal epilepsy patients.

METHODS

This case-control study was approved by the Ankara City Hospital Institutional Review Board (decision no: E2-23-3634, date: 15.03.2023). Patients diagnosed with maternal epilepsy between 2019 and 2022 were included in the study group. Randomly assigned consecutive uncomplicated healthy pregnant women constituted the control group. The data of the patients were obtained retrospectively.

Pregnant women with complete blood count (CBC) results in the first trimester of pregnancy (<14 weeks) were included. Excluded were pregnant women with alcohol and cigaret consumption, chronic diseases, drug use except for epilepsy, maternal infection, thrombophilia, and fetal structural and chromosomal anomalies.

Maternal age, gravidity, parity, and neonatal outcomes (gestational age at delivery, birth weight, and APGAR scores) were recorded as study parameters. The pregnant women's CBC parameters until the 14th week of gestation were recorded. Hemoglobin (Hb), hematocrit (Hct), Plt, white blood cell (WBC), lymphocyte (Lym), monocyte, and neutrophil levels were recorded from the CBC results. Additionally, PLR, PMR, and PNR, which are inflammatory markers, were calculated and recorded. The seizure history of patients with epilepsy during pregnancy and the antiepileptic drugs they used were recorded.

Statistical Analysis

To analyze the data, the Statistical Package for the Social Sciences 24 program was used. The conformity of the data to the normal distribution was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. As the data did not show normal distribution, non-parametric methods were used for the analysis. The Mann-Whitney U test was used to compare the parameters between the groups. Non-normally distributed data are shown as median (minimum-maximum). Categorical data are shown as numbers (n) and percentages (%). A p-value <0.05 was set as a significant.

RESULTS

One hundred thirteen pregnant epilepsy patients were included in this study. As a control group, 339 healthy pregnant women were included.

Table 1, the comparison of clinicalodemographic features and CBC results in the 1st trimester of pregnancy. No statistically significant difference was found between the groups' maternal age and the number of gravidities. As for the CBC results during the 1st trimester, whereas the Plt was 271x10^9/L in the epilepsy group, it was 249x10^9/L in the control group (p=0.029). PMR and PNR were also significantly higher in the epilepsy group accordingly (p=0.011, p=0.014 respectively). No significant difference was seen in Hb, Hct, WBC, Lym, monocytes, neutrophils, and PLR (all p>0.05).

Epilepsy patients were divided into two groups as those with seizure history during pregnancy and not. In Table 2, the comparison of epilepsy patients according to seizure history is shown. Of the 113 epilepsy patients, 50 had a seizure history during pregnancy (44.2%). No significant difference was found between epilepsy patients with or without a seizure history or not as to demographic features and CBC parameters during the 1st trimester of pregnancy (all p>0.05).

Antiepileptic drugs were questioned. Seven of the epilepsy patients received polytherapy, 94 received monotherapy, and 12 were followed without medication during pregnancy. The most commonly used drug in epilepsy patients receiving monotherapy was levetiracetam, with 56 patients (49.6%). The second most common drug used was lamotrigine (n=17). Epilepsy patients receiving monotherapy and polytherapy were compared in terms of neonatal outcomes. There was no significant difference in gestational age at birth, APGAR scores, and birth weight between these groups (all p>0.05).

DISCUSSION

Epilepsy is a neurological disease that generally has a stable course during pregnancy; however, in some patients, seizures may be aggravated and neonatal outcomes are not clear.[2] In the current study, CBC parameters and Plt indices were evaluated in pregnant epilepsy patients and compared with healthy pregnant controls. We found that Plt, PMR, and PNR was significantly higher in

Table 1. Clinicodemographic features and CBC results of epilepsy and control groups

Variables	Epilepsy group (n=113)	Control group (n=339)	p value
Age (year)	28 (18-42)	28 (17-44)	0.787
Gravidity (n)	2 (1-9)	2 (1-8)	0.935
Parity (n)	2 (1-6)	1 (0-6)	**0.001**
Hemoglobin (g/dL)	12.2 (9.3-16.5)	12.2 (8.9-15.4)	0.608
Hematocrit (%)	36.8 (28.1-44.5)	36.5 (23.2-44.9)	0.792
Platelet (x10^9/L)	271 (90-511)	249 (118-442)	**0.029**
WBC (x10^9/L)	8.83 (4.49-16.67)	9.04 (4.23-14.61)	0.346
Lymphocyte (x10^9/L)	1.88 (0.67-6.30)	1.75 (0.49-5.61)	0.271
Monocyte (x10^9/L)	0.42 (0.16-1.17)	0.42 (0.14-1.54)	0.350
Neutrophil (x10^9/L)	6.09 (1.93-14.27)	6.51 (2.47-13.05)	0.201
PLR	146.80 (60.05-402.48)	139.73 (60.08-501.82)	0.344
PMR	622.50 (249.25-2319.05)	571.43 (22.92-2635.72)	**0.011**
PNR	43.37 (16.18-264.77)	38.76 (12.48-118.34)	**0.014**

Values were given as median (minimum-maximum).
p<0.05 was considered statistically significant.
CBC: Complete blood count, WBC: White blood cell, PLR: Platelet/lymphocyte ratio, PMR: Platelet/monocyte ratio, PNR: Platelet/neutrophil ratio

MAIN POINTS

- Epilepsy is the most common chronic neurological disease with an incidence of 0.3-0.7% in pregnant women.
- Epilepsy was shown to have chronic low-grade inflammation.
- Inflammatory platelet indices may be used in combination with other parameters for the management of pregnancies complicated with epilepsy.

Table 2. Clinicodemographic features and CBC results of epilepsy patients according to seizure history during pregnancy

Variables	Seizure + group (n=50)	Seizure - group (n=63)	p value
Age (year)	28 (19-42)	27 (18-40)	0.537
Gravidity (n)	3 (1-9)	2 (1-6)	0.051
Parity (n)	2 (1-6)	2 (1-4)	0.224
Hemoglobin (g/dL)	12.1 (9.9-16.5)	12.2 (9.3-14.7)	0.722
Hematocrit (%)	36.65 (28.6-44.5)	37.1 (28.1-43.4)	0.512
Platelet ($x10^9$/L)	256 (180-487)	290 (90-511)	0.454
WBC ($x10^9$/L)	8.47 (4.49-16.67)	8.90 (4.97-14.49)	0.945
Lymphocyte ($x10^9$/L)	1.77 (0.80-3.98)	1.94 (0.67-6.30)	0.118
Monocyte ($x10^9$/L)	0.40 (0.16-0.81)	0.44 (0.18-1.17)	0.383
Neutrophile ($x10^9$/L)	6.08 (3.09-14.27)	6.09 (1.93-11.32)	0.775
PLR	142.92 (60.05-402.48)	147.18 (73.49-276.42)	0.529
PMR	622.90 (313.16-2319.05)	615.15 (249.25-1663.64)	0.801
PNR	41.49 (19.32-111.19)	46.27 (16.18-264.77)	0.481
Gestational age at birth (weeks)	38 (25-41)	38 (25-40)	0.314
Birth weight (grams)	2970 (530-3840)	3130 (690-4400)	0.148
APGAR5	9 (6-9)	9 (5-10)	0.182

Values were given as median (minimum-maximum).
$p<0.05$ was considered statistically significant.
CBC: Complete blood count, WBC: White blood cell, PLR: Platelet/lymphocyte ratio, PMR: Platelet/monocyte ratio, PNR: Platelet/neutrophil ratio

the epilepsy group during the first trimester. PLR did not differ between the groups. No significant differences were seen in terms of demographic features between the epilepsy and control groups and between epilepsy patients having seizures during pregnancy and not.

In a study conducted by Güneş and Büyükgöl,[10] inflammatory markers such as NLR, PLR, and C-reactive protein (CRP) were evaluated in patients with epilepsy during the acute phase of seizures. NLR and CRP were increased during epileptic seizures. However, the PLR did not differ between epilepsy and controls. This study evaluated non-pregnant individuals. The results were suggested to be due to the lower Plt levels in the epilepsy patients. In our study, pregnant women diagnosed with epilepsy were included, and the Plt of the epilepsy patients was shown to be higher than that of the controls. Pregnancy has a complex course in terms of adaptive and immunological processes. Although an immune process accompanies placental invasion and inflammation during the first trimester, the immune tolerance mechanism also prevents the fetus and conception material from being rejected.[16,17] Another conflicting situation during pregnancy is altered CBC parameters.[18] Epilepsy was shown to have chronic low-grade inflammation, not severe acute inflammation, suggesting stable levels of inflammatory markers.[14] In our opinion, the findings of the current study may be due to low-grade inflammation during the first trimester.

In a recently published review, patients with epilepsy had higher NLR values during the acute phase of the disease.[11] This review assumed that epileptogenesis was the result of local and systemic inflammatory responses and thought that inflammatory markers that are easily accessible may be reasonable to be studied in epilepsy patients to help clinicians better follow up epilepsy patients under control. Conversely, Faruk Ozdemir et al.[12] evaluated preoperative inflammatory markers in epilepsy patients undergoing surgery and found no statistical difference as to NLR and PLR. They concluded that systemic inflammatory markers were not to be used as indexes in epilepsy patients. This study included some epilepsy patients (n=21). However, all these studies were conducted in the non-pregnant population and in the acute phase of epilepsy. The literature lacks information on pregnant women with epilepsy regarding inflammatory markers.

In our study, patients with epilepsy were mostly under monotherapy, and the most common drug used was levetiracetam to almost half of the patients concurrent with the literature.[19] No major congenital malformations were detected in epilepsy patients. All pregnant women enrolled in this study had a live birth. Although 50 patients (44.25%) had seizures during pregnancy, no significant difference in terms of neonatal outcomes suggests that the epilepsy was under control.

Study Limitations

The main strength of our study was the high number of epilepsy patients (n=113) and healthy pregnant controls (n=339). Our hospital is a referral center for complicated and high-risk pregnancies. Inflammatory markers were evaluated in the first trimester to determine whether there was a relationship between adverse neonatal outcomes. However, the study was conducted retrospectively. Another limitation was the lack of CBC results at the time of labor and/or delivery.

CONCLUSION

In conclusion, we believe that pregnant women with epilepsy have low-grade inflammation during the first trimester. Pregnancy has a complex course with altered CBC parameters. Inflammatory Plt indices may be used in combination with other parameters for the management of pregnancy. Further studies are required.

Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital Institutional Review Board (decision no: E2-23-3634, date: 15.03.2023).

Informed Consent: Retrospective case-control study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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REFERENCES

1. Chen D, Hou L, Duan X, Peng H, Peng B. Effect of epilepsy in pregnancy on fetal growth restriction: a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2017;296(3):421-427. [Crossref]
2. Borgelt LM, Hart FM, Bainbridge JL. Epilepsy during pregnancy: focus on management strategies. *Int J Womens Health*. 2016;8:505-517. [Crossref]
3. Seiffert E, Dreier JP, Ivens S, et al. Lasting blood-brain barrier disruption induces epileptic focus in the rat somatosensory cortex. *J Neurosci*. 2004;24(36):7829-7836. [Crossref]
4. Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain*. 2005;128(Pt 3):454-471. [Crossref]
5. Marchi N, Granata T, Alexopoulos A, Janigro D. The blood-brain barrier hypothesis in drug resistant epilepsy. *Brain*. 2012;135(Pt 4):e211. [Crossref]
6. Marchi N, Granata T, Janigro D. Inflammatory pathways of seizure disorders. *Trends Neurosci*. 2014;37(2):55-65. [Crossref]
7. Tanacan A, Oluklu D, Laleli Koc B, et al. The utility of systemic immune-inflammation index and systemic immune-response index in the prediction of adverse outcomes in pregnant women with coronavirus disease 2019: Analysis of 2649 cases. *J Obstet Gynaecol Res*. 2023;49(3):912-919. [Crossref]
8. Ersak DT, Tanacan A, Laleli Koç B, Sınacı S, Kara Ö, Şahin D. The utility of complete blood parameter indices to predict stillbirths. *J Matern Fetal Neonatal Med*. 2023;36(1):2183747. [Crossref]
9. Turgut E, Yildirim M, Sakcak B, Ayhan SG, Tekin OM, Sahin D. Predicting miscarriage using systemic immune-inflammation index. *J Obstet Gynaecol Res*. 2022;48(3):587-592. [Crossref]
10. Güneş M, Büyükgöl H. Relationship between generalized epileptic seizure and neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and neutrophil mediated inflammation. *Int J Neurosci*. 2020;130(11):1095-1100. [Crossref]
11. Hosseini S, Mofrad AME, Mokarian P, et al. Neutrophil to Lymphocyte Ratio in Epilepsy: A Systematic Review. *Mediators Inflamm*. 2022;2022:4973996. [Crossref]
12. Faruk Ozdemir A, Kemerdere R, Orhan B, et al. Serum endocan and preoperative systemic inflammatory markers in patients with epilepsy. *Neurochirurgie*. 2020;66(1):29-35. [Crossref]
13. Kayhan A, Korkmaz TS, Baran O, Kemerdere R, Yeni SN, Tanriverdi T. Preoperative Systemic Inflammatory Markers in Different Brain Pathologies: An Analysis of 140 Patients. *Turk Neurosurg*. 2019;29(6):799-803. [Crossref]
14. Vieira ÉLM, de Oliveira GNM, Lessa JMK, et al. Peripheral leukocyte profile in people with temporal lobe epilepsy reflects the associated proinflammatory state. *Brain Behav Immun*. 2016;53:123-130. [Crossref]
15. Morkavuk G, Koc G, Leventoglu A. Is the differential diagnosis of epilepsy and psychogenic nonepileptic seizures possible by assessing the neutrophil/lymphocyte ratio? *Epilepsy Behav*. 2021;116:107736. [Crossref]
16. Cavalcante MB, Sarno M, Araujo Júnior E, Da Silva Costa F, Barini R. Lymphocyte immunotherapy in the treatment of recurrent miscarriage: systematic review and meta-analysis. *Arch Gynecol Obstet*. 2017;295(2):511-518. [Crossref]
17. Meuleman T, Lashley LE, Dekkers OM, van Lith JM, Claas FH, Bloemenkamp KW. HLA associations and HLA sharing in recurrent miscarriage: A systematic review and meta-analysis. *Hum Immunol*. 2015;76(5):362-373. [Crossref]
18. Whittaker PG, Macphail S, Lind T. Serial hematologic changes and pregnancy outcome. *Obstet Gynecol*. 1996;88(1):33-39. [Crossref]
19. Koc G, Keskin Guler S, Karadas O, Yoldas T, Gokcil Z. Fetal safety of levetiracetam use during pregnancy. *Acta Neurol Belg*. 2018;118(3):503-508. [Crossref]