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First and second trimester laboratory changes and perinatal outcomes in pregnant women with epilepsy

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ABSTRACT

Aims: The aim of this study is to comprehensively evaluate the demographic, first-second trimester laboratory parameters and perinatal outcomes in pregnant women with epilepsy.

Methods: The study had a total of 73 pregnant women with epilepsy, along with 149 healthy pregnant women. Demographic data, first-second trimester laboratory parameters, seizures during pregnancy, the administration of antiepileptic medicines and perinatal outcomes were documented from September 2022 to 2023. Pregnant women with epilepsy were formed into subgroups according to whether they had seizures during pregnancy or not and whether they used antiepileptic drugs, and first- and second-trimester laboratory parameters were compared between the groups. Furthermore, univariate and multivariate linear regression analysis investigated the relationship between these parameters with the composite adverse neonatal outcomes (CANO).

Results: In the study, 72.7% of pregnant women diagnosed with epilepsy were receiving antiepileptic treatment (75.4% monotherapy and 24.6% polytherapy). The incidence of seizures during pregnancy was 38.3%. The epilepsy group exhibited statistically significant differences from the control group in the following areas: gestational age at delivery, preterm birth rate, cesarean section rate, birth weight, neonatal head circumference, APGAR score <7 at the 1st and 5th minutes, and CANO. The Neutrophil to Lymphocyte Ratio (NLR) was significantly higher in the epilepsy group in the second trimester ($p=0.027$), and the monocyte to lymphocyte ratio (MLR) was significantly higher in the first trimester in the epilepsy group ($p<0.001$). Upon comparing who experienced seizures during pregnancy and those who did not, no significant difference was found between the two groups. In the univariate logistic regression model, it was determined that having a seizure during pregnancy was a significant predictor, indicating a higher likelihood of developing perinatal complications. Multivariate linear regression analysis showed no significant correlation.

Conclusion: The laboratory results of pregnant women with epilepsy during the first and second trimesters show differences compared to healthy pregnant women. Pregnant women diagnosed with epilepsy were associated with a higher risk of preterm delivery and giving birth to newborns with lower birth weight and head circumference. These differences may have significance in the follow-up and care of pregnant women with epilepsy.

Keywords: Epilepsy, perinatal outcomes, first- and second-trimester laboratory parameters

INTRODUCTION

Antenatal care, antiepileptic drug use, seizure control and perinatal outcomes in women with epilepsy during pregnancy are an interesting and important topic that has not yet been fully elucidated for all periods. Epilepsy is a long-term neurological disease characterized by recurrent seizures and occurs in approximately 1% of the general population worldwide.[1,2] The condition impacts approximately 6.85 cases per 1000 women within the context of gender and affecting an estimated 15 million women in the reproductive age group globally.[3,4] Treatment of pregnant women with epilepsy requires a delicate balance between maintaining control of maternal seizures and the potential adverse effects of antiepileptic drugs on the developing fetus. Pregnancy with epilepsy is associated with an increased risk of adverse maternal and perinatal outcomes. The risks encompassed in this context are preeclampsia, preterm birth, stillbirth, fetal growth restriction, congenital abnormalities, and maternal mortality.[5] This highlights the importance of good prenatal care and the need to better understand the mechanisms underlying these risks so that preventive interventions can be designed.

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In animal studies, inflammation has been found to be involved in the initiation and progression of epilepsy and in an animal model of epilepsy, infiltration of leukocytes, lymphocytes, and monocytes was identified in certain regions of the brain.[6,7] The development of epilepsy may be influenced by both local and systemic inflammatory responses, as evidenced by elevated levels of chemokines and cytokines in the cerebrospinal fluid and peripheral blood of individuals with epilepsy. In a systematic review by Hosseini et al.,[8] it was determined that inflammation plays a role in epilepsy and that a high neutrophil to lymphocyte ratio (NLR) value may be a good biomarker for inflammation and therefore epilepsy.[9] There are a limited number of studies in the literature showing the effects of changes in maternal serum markers in the first and second trimester on the number of seizures during pregnancy and perinatal outcomes in pregnant women with epilepsy.[10-12] Moreover, alterations in laboratory parameters throughout the first and second trimesters might offer vital information regarding the well-being of both the mother and the developing fetus.[13-15] We aimed to investigate whether there is a relationship between maternal first and second trimester serum parameters and seizure occurrence and perinatal outcomes.

METHODS

This retrospective case-control study includes 73 pregnant women with epilepsy and 149 healthy pregnant women whose follow-up, treatment and births took place between 2022 and 2023 at Ankara Etlik City Hospital, a tertiary center where approximately 12,500 births occur annually. Ethical approval was received for this study from Ankara Etlik City Hospital Clinical Researches Ethics Committee (Decision No: AESH-EK1-2023-170). This study adhered to the criteria outlined in the Declaration of Helsinki.

The control group was randomly selected among healthy pregnant women. Exclusion criteria were using medications other than antiepileptic drugs, smoking, having any systemic disease, and having multiple pregnancies. The pregnant woman's age, gravity, parity, body-mass index (BMI), time since epilepsy diagnosis, use of antiepileptic drugs during pregnancy (monotheraphy, politheraphy), whether and how many seizures during pregnancy, gestational age at delivery, type of birth, neonatal birth weight, 1st and 5th minutes APGAR score, and neonatal intensive care unit (NICU) admission were obtained from the hospital's electronic medical record system. Composite adverse neonatal outcome was defined as the presence of at least one of the following situations: respiratory distress syndrome (RDS), 5th minute APGAR score <7, and NICU admission. Laboratory parameters such as first and second trimester white blood cell counts (WBC), lymphocyte, neutrophil, monocyte, hemoglobin, platelet were obtained from maternal serum complete blood count results. NLR was calculated by dividing the absolute number of neutrophil by the absolute number of lymphocyte at each time point. Monocyte to lymphocyte ratio (MLR) was calculated by dividing the monocyte count by lymphocyte count, and Platelet to lymphocyte ratio (PLR) by dividing the platelet count by lymphocyte count. All these parameters were compared between pregnant women with epilepsy and healthy control pregnant women. Moreover pregnant women with epilepsy were divided into subgroups according to the presence or absence of seizures during pregnancy and with and without antiepileptic treatment. Then, first-second trimester laboratory parameters compared with each other. The impact of various epilepsy characteristics on pregnancy was investigated using univariable and multivariable logistic regression analyses.

Statistical Analysis

This study involved the analysis of demographic, neonatal, and ultrasonographic data of pregnant women with epilepsy. Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, N.Y., USA). For demographic and ultrasonographic data, group comparisons were made using median and interquartile range (IQR) values. Continuous variables were analyzed using both the Mann-Whitney U test and student's t-test to assess differences between groups. Categorical variables were presented as numbers and percentages and analyzed using the Chi-square test. Univariable and multivariable logistic regression analyses were utilized to investigate the effects of various epilepsy characteristics on pregnancy outcomes. In the univariable logistic regression analysis, each variable was examined individually to identify potential predictors. The multivariable logistic regression analysis was then employed to adjust for confounders and to ascertain the independent impact of each variable. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed to evaluate the risk associated with each factor. The significance level was set at $p<0.05$ for all analyses, and results were reported with a 95% confidence interval.

RESULTS

The patient cohort is presented in Table 1. The study evaluated 73 pregnant women diagnosed with epilepsy. Among these, 72.7% (n=53) were undergoing epilepsy treatment, with 75.4% (n=40) of this group receiving monotherapy and 24.6% (n=13) on polytherapy. The proportion of women not receiving treatment was 27.3% (n=20). The incidence of seizures during pregnancy was observed in 38.3% (n=28) of the subjects, and there were no cases of status epilepticus (0.0%).

Table 1. Patient cohort of pregnant women with epilepsy

Pregnant women with epilepsy, n (%)	n=73 (100)
Time since epilepsy diagnosis (year), median (IQR)	8.0 (10.0)
Active treatment	
No theraphy, n (%)	20 (27.3)
Yes theraphy	53 (72.7)
Monotheraphy, n (%)	40 (75.4)
Politheraphy, n (%)	13 (24.6)
Seizures during pregnancy, n (%)	28 (38.3)
Number of seizures during pregnancy, median (IQR)	0.0 (1.0)
Status epilepticus, n (%)	0 (0.0)

The comparison of demographic, clinical, and perinatal outcomes between pregnant women with epilepsy and a

control group is displayed in Table 2. The maternal age, gravidity, parity, BMI were similar between the groups. When examining gestational age at delivery, the median was 38 weeks (IQR: 2.0) in the epilepsy group and 39 weeks (IQR: 2.0) in the control group, with the difference being statistically significant (p<0.001). The rate of preterm birth (<37 weeks) was 27.4% in the epilepsy group, while no cases were reported in the control group (p<0.001). Regarding the mode of delivery, 26% of the epilepsy group had vaginal births, and 74% had cesarean sections. In contrast, the control group had 49.7% vaginal and 50.3% cesarean deliveries, with this difference being statistically significant (p<0.001). The birth weight was 2950 grams (IQR: 920) in the epilepsy group and 3240 grams (IQR: 580) in the control group, also showing a significant difference (p<0.001). Neonatal head circumference was 34.0 cm (IQR: 2.00) in the epilepsy group and 35.0 cm (IQR: 1.00) in the control group, with this difference being significant (p<0.001). Additionally, the rate of newborns with an APGAR score <7 at 1 minute was 11% in the epilepsy group compared to 2% in the control group (p=0.004). The rate of APGAR scores <7 at 5 minutes was observed at 6.8% only in the epilepsy group (p=0.001). The rate of CANO was 21.9% in the epilepsy group compared to 3.4% in the control group, which was also statistically significant (p<0.001).

Table 2. Demographic data, clinical and perinatal characteristics of the patients

Median (IQR), n (%)	Epilepsy, n=73	Control, n=149	p value
Maternal age (year), median (IQR)	28.0 (7.00)	27.0 (7.00)	0.712
BMI (kg/m^2), median (IQR)	28.0 (7.21)	29.3 (6.75)	0.070
Gravidity, median (IQR)	2 (2)	2 (2)	0.213
Parity, median (IQR)	1 (1)	1 (2)	0.104
Gestational age at delivery (week), median (IQR)	38.0 (2.0)	39.0 (2.0)	<0.001
Preterm birth (<37 weeks) n (%)	20 (27.4)	0 (0.0)	<0.001
Birth type, n (%)			
Vaginal delivery	19 (26.0)	74 (49.7)	<0.001
Cesarean section	54 (74.0)	75 (50.3)	
Birth weight (gram), median (IQR)	2950 (920)	3240 (580)	<0.001
Neonatal head circumference, median (IQR)	34.0 (2.00)	35.0 (1.00)	<0.001
APGAR 1th min. score <7, n (%)	8 (11.0)	3 (2.0)	0.004
APGAR 5th min. score <7, n (%)	5 (6.8)	0 (0.0)	0.001
CANO, n (%)	16 (21.9)	5 (3.4)	<0.001

IQR: Inter quantile range, BMI: Body-mass index, IVF: In vitro fertilization, APGAR: Appearance, pulse, grimace, activity and respiration, CANO: Composite adverse neonatal outcome

Table 3 presents the comparison of first and second trimester laboratory characteristics between pregnant women with epilepsy and the control group. In the first trimester, the hemoglobin levels were 12.3 g/dL in the epilepsy group and 12.8 g/dL in the control group, showing a significant difference (p<0.001). In the second trimester, hemoglobin levels dropped to 11.3 g/dL in the epilepsy group, compared to 12.0 g/dL in the control group, with this change also being significant (p=0.002). WBC showed significant differences between the groups in the first trimester (p=0.023), which continued into the second trimester (p=0.020). Neutrophil counts were significantly higher in the epilepsy group during the second trimester compared to the control group (p=0.001). Monocyte counts only showed a significant difference in the first trimester between the epilepsy and control groups (p<0.001), with no significant difference found in the second trimester (p=0.539). Additionally, the neutrophil to lymphocyte ratio (NLR) was significantly higher in the epilepsy group in the second trimester (p= 0.027), and the monocyte to lymphocyte ratio (MLR) was significantly higher in the first trimester in the epilepsy group (p<0.001).

Table 3. Comparison of 1st and 2nd trimester laboratory characteristics in epilepsy and control groups

Median (IQR)	Epilepsy, n=73		Control, n=149			
	1st trimester	2nd trimester	1st trimester	2nd trimester	p1	p2
Hemoglobin (g/dl)	12.3 (1.70)	11.3 (1.30)	12.8 (1.10)	12.0 (1.35)	<0.001	0.002
WBC (*10^3/mm^3)	8.97 (3.69)	10.50 (3.11)	8.19 (2.54)	9.27 (3.12)	0.023	0.020
Neutrophil (*10^3/mm^3)	5.89 (2.61)	7.52 (3.19)	5.67 (2.35)	6.63 (2.84)	0.067	0.001
Lymphocyte (*10^3/mm^3)	2.18 (0.970)	1.90 (0.690)	1.93 (0.790)	1.90 (0.770)	0.109	0.884
Monocyte (*10^3/mm^3)	0.570 (0.180)	0.630 (0.240)	0.450 (0.200)	0.620 (0.295)	<0.001	0.539
Platelet (*10^3/mm^3)	260 (89.0)	244 (73.0)	261 (85.0)	244 (74.5)	0.328	0.966
NLR	2.91 (1.62)	4.08 (2.54)	2.99 (1.36)	3.57 (1.78)	0.574	0.027
PLR	135 (63.6)	134 (56.4)	137 (63.8)	120 (53.8)	0.238	0.299
MLR	0.311 (0.108)	0.321 (0.149)	0.241 (0.120)	0.327 (0.144)	<0.001	0.363

WBC: White blood cell counts, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio

Table 4 shows the results comparing pregnant women with epilepsy who experienced seizures during pregnancy with those who did not, for first and second trimester laboratory characteristics. The monocyte ratio in the second trimester was 0.660 in those who experienced seizures, compared to 0.620 in those who did not, with a p-value of 0.068, indicating slightly higher monocyte ratios in those who experienced seizures, although not reaching statistical significance.

In the study, pregnant women with epilepsy, whether receiving treatment or not, were compared, and the laboratory parameter differences were investigated in Table 5. No statistically significant differences were found between the treated and untreated groups.

The impact of various epilepsy characteristics on pregnancy was investigated using univariable and multivariable logistic regression analyses. The analyses considered factors such as experiencing seizures during pregnancy, the time since epilepsy diagnosis, the number of seizures during pregnancy, and the type of treatment (polytherapy or monotherapy) used (Table 6). The condition of experiencing seizures during pregnancy was found to be a significant predictor in the

Table 4. Comparison of 1st and 2nd trimester laboratory characteristics in epileptic pregnant women with and without seizures during pregnancy

	With seizures, n=28		Without seizures, n=45			
Median (IQR)	1st trimester	2nd trimester	1st trimester	2nd trimester	p1	p2
Hemoglobin (g/dl)	12.3 (2.25)	11.3 (1.70)	12.3 (1.70)	11.5 (1.30)	0.945	0.811
WBC (*10³/mm³)	10.80 (4.36)	10.70 (3.85)	8.88 (3.76)	10.40 (3.25)	0.171	0.321
Neutrophil (*10³/mm³)	6.22 (3.01)	7.46 (3.20)	5.88 (2.64)	7.73 (2.92)	0.304	0.485
Lymphocyte (*10³/mm³)	2.30 (1.000)	1.90 (0.810)	1.96 (0.810)	1.84 (0.800)	0.231	0.518
Monocyte (*10³/mm³)	0.585 (0.178)	0.660 (0.325)	0.570 (0.230)	0.620 (0.220)	0.896	0.068
Platelet (*10³/mm³)	266 (93.5)	250 (101.0)	260 (79.0)	244 (59.0)	0.883	0.834
NLR	2.89 (1.64)	3.88 (3.83)	2.94 (1.62)	4.45 (1.93)	0.878	0.887
PLR	134 (53.3)	132 (32.5)	136 (71.3)	134 (72.8)	0.367	0.860
MLR	0.305 (0.092)	0.361 (0.131)	0.325 (0.156)	0.315 (0.141)	0.450	0.218

WBC: White blood cell counts, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio

Table 5. Comparison of 1st and 2nd trimester laboratory characteristics according to treatment requirement in the epilepsy group

	No theraphy, n=20		Yes theraphy, n=53			
Median (IQR)	1st trimester	2nd trimester	1st trimester	2nd trimester	p1	p2
Hemoglobin (g/dl)	12.3 (1.20)	11.3 (0.85)	12.3 (1.80)	11.5 (1.40)	0.607	0.581
WBC (*103/mm³)	9.68 (4.87)	10.70 (4.99)	8.96 (3.41)	10.40 (2.78)	0.536	0.697
Neutrophil (*10³/mm³)	6.04 (3.39)	7.88 (3.82)	5.89 (2.33)	7.29 (2.94)	0.951	0.621
Lymphocyte (*10³/mm³)	2.21 (0.765)	1.90 (0.715)	2.01 (.1.000)	1.90 (0.660)	0.715	0.887
Monocyte (*10³/mm³)	0.570 (0.318)	0.600 (0.395)	0.580 (0.170)	0.630 (0.230)	0.647	0.748
Platelet (*10³/mm³)	272 (86.5)	250 (73.3)	254 (77.0)	243 (68.0)	0.669	0.565
NLR	2.89 (1.36)	4.51 (1.68)	2.99 (1.65)	3.82 (2.61)	0.516	0.432
PLR	138 (82.1)	136 (72.4)	135 (57.7)	129 (54.5)	1.000	0.462
MLR	0.282 (0.167)	0.308 (0.177)	0.318 (0.101)	0.321 (0.140)	0.790	0.867

WBC: White blood cell counts, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio

Table 6. Univariable and multivariable logistic regression analysis of epilepsy characteristics

	Univariable LR			Multivariable LR		
	OR	CI	p value	OR	CI	p value
Seizures during pregnancy	3.611	1.136-11.473	0.029	3.511	0.771-15.979	0.104
Time since epilepsy diagnosis (year)	0.961	0.878-1.050	0.379			
Number of seizures during pregnancy	1.178	0.837-1.658	0.348			
Politheraphy versus Monotheraphy	3.542	0.860-14.577	0.080	2.582	0.583-11.428	0.211

LR: Logistic regression, OR: Odds ratio, CI: Confidance interval

univariable logistic regression model; those who experienced seizures had a higher chance of complications compared to those who did not (OR=3.611, CI=1.136-11.473, p=0.029). However, in the multivariable model, this relationship lost its significance (OR=3.511, CI=0.771-15.979, p=0.104), indicating that when considering other factors, experiencing seizures during pregnancy does not significantly predict complications. The duration since epilepsy diagnosis was not found to be a significant predictor in the univariable regression model (OR=0.961, CI=0.878-1.050, p=0.379), suggesting that the duration of epilepsy diagnosis does not affect the risk of complications during pregnancy. The number of seizures experienced during pregnancy was also not a significant predictor in the univariable model (OR=1.178, CI=0.837-1.658, p=0.348). Regarding the type of treatment, a nearly significant relationship was found between those undergoing polytherapy compared to monotherapy in the univariable model (OR=3.542, CI=0.860-14.577, p=0.080); however, this relationship was not significant in the multivariable model (OR=2.582, CI=0.583-11.428, p=0.211).

DISCUSSION

In the study, MLR exhibited significant differences in the first trimester and NLR were significantly different in the second trimester between pregnant women with epilepsy and the control group. Upon comparing the first and second trimester laboratory characteristics of pregnant women with epilepsy who experienced seizures during pregnancy and those who did not, and with and without treatment, no significant difference was found between the two groups.

NLR is a dependable, cost-effective, and simple indicator of the immune response. NLR has been observed to be elevated throughout the acute and subacute stages of seizures compared to individuals without any health conditions. An elevated NLR is widely recognized as a biomarker for both inflammation and epilepsy.[9] In a recent study, significant differences ($p<0.05$) were observed in after remission monocyte, lymphocyte, platelet, NLR and MLR levels between adult patients with convulsive status epilepticus and a healthy control group.[16] There is a dearth of information in the literature addressing inflammatory indicators in pregnant women with epilepsy. Bergen et al.[12] found no significant difference in the third trimester NLR value between pregnant women with epilepsy and the control group. In our study, we found that there was no significant difference in the NLR value during the first and second trimesters between pregnant women with epilepsy who received antiepileptic treatment and those who did not, as well as between those who experienced seizures during pregnancy and those who did not. However, we did observe a significantly higher NLR value during the second trimester in pregnant women with epilepsy compared to the control group of pregnant women without epilepsy. In our study, while a significant difference in MLR level was detected between pregnant women diagnosed with epilepsy and the control group in the first trimester, no significant difference was detected in the second trimester. Our study is is the first to evaluate parameters associated with NLR, MLR, PLR levels during the first and second trimesters in epilepsy and pregnancy. If a relationship between changing laboratory

parameters during pregnancy and epileptic seizure frequency and perinatal outcomes is established, these parameters could potentially serve as useful and accessible markers for monitoring and managing epilepsy during pregnancy.

Research has consistently shown that exposure to antiepileptic drugs during pregnancy is linked to a higher likelihood of impaired fetal growth, lower birth weight in relation to gestational age, and smaller head circumference at birth, particularly in polytherapy.[17-20] In the MONEAD study, they found no difference in preterm birth, 5-minute APGAR <6, neonatal intensive care unit admission, gestational age, or any growth measurement between babies born to healthy and epileptic pregnant women, and concluded that epileptic drug use was not associated with adverse early neonatal outcomes.[21] In our current study, birth weight, newborn head circumference, 1st and 5th minute APGAR score <7, CANO showed significant differences in the epilepsy group compared to the control group.

In our study, the majority of epilepsy patients were receiving monotherapy (75.4%), and in line with the literature. Major congenital malformation was detected in only 4 patients with epilepsy and these patients were excluded from the study. No fetal or neonatal mortality was observed in the pregnant women included in this study. It has been shown that the frequency of seizures increases in 25-30% of pregnant women diagnosed with epilepsy.[22] In our study, among the pregnant women diagnosed with epilepsy, 28 (38.3%) had seizures during pregnancy. When the effects of factors such as experiencing seizures during pregnancy, time since the diagnosis of epilepsy, number of seizures during pregnancy, and the type of treatment used (polytherapy or monotherapy) on pregnancy with epilepsy were investigated using univariate and multivariate logistic regression analyses; In the univariate logistic regression model, having a seizure during pregnancy was found to be a significant predictor; the likelihood of developing complications was higher. However, the fact that this relationship lost its significance in the multivariate model shows that having a seizure during pregnancy does not significantly predict complications when other factors are taken into account.

Limitations

This study is limited by its retrospective design, being conducted at a single center, and having a small sample size. However, the strengths of this study is its detailed analysis of the relationship between first and second trimester laboratory parameters, seizure activity during pregnancy, antiepileptic drug use, and perinatal outcomes in pregnant women with epilepsy.

CONCLUSION

The laboratory results of pregnant women with epilepsy during the first and second trimesters show differences compared to healthy pregnant women. Pregnant women with epilepsy were associated with a higher risk of preterm delivery and giving birth to newborns with lower birth weight and head circumference. These differences may have significance in the follow-up and care of pregnant women. Prospective, large population studies are needed to reveal the relationship between seizures, antiepileptic drug use, perinatal outcomes and laboratory parameters in pregnant women with epilepsy.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital No. 1 Clinical Researches Ethics Committee (Decision No: AESH-EK1-2023-170).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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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