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Pregnancy and epilepsy: a retrospective analysis of 46 patients, and comparison of their perinatal outcomes with healthy pregnant women

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Abstract

Objective: The aim of the study was to present demographic, clinical, and perinatal outcomes of pregnant women with epilepsy and investigate the differences between epileptic and healthy pregnants.

Methods: The study group included 46 pregnant women with a diagnosis of epilepsy, and the control group had 126 pregnant women without any health problems. Data including demographic, clinical, and perinatal outcomes of all the pregnant women in this study were obtained from the archive of the hospital and electronic records. Data were statistically compared.

Results: The mean age of epilepsy and the control group were 27.5±5.6 and 30±6.8, respectively. Epilepsy duration of patients in the study group was 3.58±2.21 years. Twenty-six patients with epilepsy took folic acid before pregnancy, while 10 of them were treated after pregnancy. Eighteen (39%) patients in epilepsy group had a seizure during pregnancy. The most frequent seizures were during the first trimester (50%), and none of the patients had postpartum seizures in the early period. All patients received antiepileptic drugs. Thirty-one (67.4%) patients were treated with monotherapy and others took polytherapy. The most commonly used drug was carbamazepine (41.3%). In patients with epilepsy, age, gravidity, and parity were significantly lower, and the abortion was significantly higher than controls. No significant difference was observed between groups in terms of pregnancy related complications, cesarean section, fetal weight, fetal length, 1st and 5th minute Apgar scores at birth, and the prevalence of fetal malformation during delivery. Congenital malformations were present in 5 (10.8%) newborns (ventriculomegaly, hydrocephaly, cleft lip-palate, and cardiac anomalies) in the epileptic group and in 4 (3.1%) infants (non-immune hydrops, skeletal dysplasia, and gastroschisis) in the control group.

Conclusion: Although pregnancy outcomes in women with epilepsy are good, they should be informed for the potential risks of epilepsy before becoming pregnant and the necessary changes in treatment should be made during this period. In the process of pregnancy and labor, they should be followed by neurologists.

Key words: Congenital anomalies, epilepsy, pregnancy

Gebelik ve epilepsi: 46 olgunun retrospektif analizi ve perinatal sonuçlarının sağlıklı gebelerle karşılaştırılması

Amaç: Epilepsili gebelere ait demografik, klinik ve perinatal sonuçları sunmak ve bunların sağlıklı gebelerle arasındaki farkları araştırmaktır.

Yöntem: Epilepsi tanısı alan 46 gebe çalışma, hiçbir sağlık problemi olmayan 126 gebe kontrol grubunu oluşturdu. Çalışma kapsamına dahil edilen gebelere ait demografik, klinik ve perinatal sonuçlarla ilişkili bilgiler, hastanemize ait arşivden ve elektronik kayıtlardan elde edildi. Veriler istatistiksel olarak karşılaştırıldı.

Bulgular: Epilepsi ve kontrol grubunda yaş ortalaması sırasıyla 27.5±5.6 ve 30±6.8 olarak bulundu. Çalışma grubundaki hastaların epilepsi süresi 3.58±2.21 yıldı. Epilepsili hastaların 26'sı gebelik öncesi ve 10'u gebe kaldıktan sonra folik asit aldı. Epilepsi grubunda 18 (%39) hasta, gebelikleri sırasında nöbet geçirdi. En sık nöbet (%50) ilk trimesterde olurken, post-partum erken dönemde hiçbir hasta epileptik nöbet geçirmedi. Hastaların hepsinin antiepileptik ilaç aldığı saptandı. Otuz biri (%67.4) monoterapi ve diğerleri (% 73.9) politerapi ile tedavi edildi. En sık kullanılan ilaç karbamazepin (%41.3) idi. Epilepsi grubunda kontrollere göre yaş, gravida, parite anlamlı düşük, abortus anlamlı yüksekti. Gebelik bağlı komplikasyon, sezaryen ile doğum, fetal ağırlık, fetal boy, 1. ve 5. dakika apgar skorları, doğumda fetal malformasyon görülme sıklığı açısından her iki grup arasında anlamlı fark görülmedi. Konjenital malformasyon epileptik grupta 5 (%10.8) yenidoğanda (ventrikülomegali, hidrosefali, yarık damak-dudak, kardiyak anomali), kontrol grubunda ise 4 (%3.1) yenidoğanda (non-immun hidrops, iskelet displazisi, gastroşizis) mevcuttu.

Sonuç: Epilepsili kadınlarda gebelik sonuçları iyi olmasına rağmen, epilepsiye bağlı potansiyel risklerden dolayı gebe kalmadan önce bilgilendirilmeleri, gerekli olan tedavi değişikliklerinin bu dönemde yapılması gerekir. Bu kadınlar gebelik ve doğum sürecinde ise perinatoloji ve nöroloji uzmanları ile birlikte takip edilmelidirler.

Anahtar sözcükler: Gebelik, epilepsi, konjenital anomali.

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Introduction

Epilepsy during pregnancy is determined as a high risk. Since a significant number of women with epilepsy are at their reproductive period, it is the most frequent neurological disease during pregnancy after migraine. It is considered that 0.3-0.5% of pregnancies are accompanied by epilepsy.[1] It is reported that there is an increase in the risks of abortus, stillbirth, preterm labor, low birth weight, intrauterine growth retardation, and mental and motor retardation risks in newborn during pregnancies with epilepsy.[2,3] Besides, an increase is observed in maternal complications such as hypertensive diseases, antepartum hemorrhage, operative and interventional labor.

The increase in epileptic seizures during pregnancy about 1/3, association of antiepileptic drugs with the increase of fetal malformations are other concerns.[4] Therefore, epilepsy and pregnancy are the conditions requiring close follow-up and knowledge together with neurology in order to obtain positive maternal and fetal outcomes.

In this study, we aimed to present clinical and perinatal outcomes of pregnants known to have epilepsy before pregnancy and to research whether there is a difference or not between epileptic and healthy pregnants in terms of maternal and perinatal outcomes.

Method

This study was carried out in the Gynecology and Obstetric Clinic of Medical Faculty of Dicle University. The study was approved by Ethics Committee of Dicle University. The study was conducted on 46 pregnants diagnosed with epilepsy who were followed-up and delivered in our clinic between January 2007 and June 2012. The control group consisted of 126 healthy pregnants chosen randomly who were with ICD code pregnancy, matched with epilepsy group for their gestational week, and did not have epilepsy and/or any other systemic disease. The randomization in the control group was done by taking pregnants from computer records who delivered on Mondays and Fridays. The data of patients were obtained from patient files and electronic records in hospital archive. Cases with suspected epilepsy history were excluded from the study. The demographical data of patients such as age, gravida, parity and how many years they have epilepsy, seizure numbers and times during pregnancy, antiepileptic drugs AEDs used before pregnancy and folic acid prophylaxis. Among perinatal outcomes, delivery type, gestational weeks, birth weights and 1st and 5th minute Apgar scores were addressed as well as fetal malformations, abortus, preterm labor, intrauterine growth retardation, intrauterine death, early neonatal death and early neonatal problems.

For statistical analysis, data was analyzed on SPSS (Statistical Package for Social Sciences) for Windows 15.0 (SPSS, Inc., Chicago, IL, USA), Epi info and Excel software. It was checked whether numerical data was distributed in a normal way by Kolmogorov-Smirnov test. Mann-Whitney U, Student t and chi-square tests were used for statistical analysis of data between two groups. Results were considered statistically significant when they are within 95% confidence interval and when $p<0.05$.

Results

Forty-six patients diagnosed with epilepsy and pregnancy, and 126 patients not having any systemic disease that may complicate pregnancy were included into the study. In the patient group, mean age was 27.5±5.6 years and mean epilepsy period was 3.58±2.21 years. It was found out that only 26 of patients referred to a neurologist or obstetrician before pregnancy, and rest of them after pregnancy. It was learnt that 36 of epilepsy patients received prophylactic folic acid replacement, and 26 of these patients began folic acid treatment before pregnancy (patients receiving consultancy), and 10 of them after pregnancy. It was found out that all of the patients received AEDs, that 31 of them (67.4%) received monotherapy and others (32.6%) received polytheraphy. The most frequently used drug was carbamazepine (41.3%) (**Table 1**).

In the epilepsy group, 18 (39%) patients had seizure during pregnancy. All of the patients who had seizure

Table 1. Distribution of anti-epileptic drugs used during pregnancy.

Drug	n	%
Carbamazepine	19	41.3
Sodium valproate	7	15.2
Oxcarbazepine	5	10.9
Levetiracetam	3	6.5
Carbamazepine + Sodium valproate	8	17.4
Carbamazepine + Levetiracetam	1	2.2
Oxcarbazepine + Sodium valproate	3	6.5

during pregnancy were those who did not have consultancy before pregnancy. During pregnancy, seizures were mostly seen during the first trimester (50%) and it was seen in the second trimester at the lowest rate (**Table 2**).

Table 2. Characteristics of patients who had seizure during their pregnancies (n=18).

	n
Gestational period	
1st trimester	9
2nd trimester	4
3rd trimester	5
Seizure times	
1 time	13
2 times	4
≥3 times	1
Drugs used	
Carbamazepine	7
Sodium valproate	3
Oxcarbazepine	1
Carbamazepine + Sodium valproate	6
Oxcarbazepine + Sodium valproate	1

Epileptic seizure was not observed during post-partum early period in none of the pregnants followed up. When demographic data of the epilepsy and control groups are compared, it was found that age, gravida, parity were significantly low and abortus was significantly high in the epilepsy group compared to the control group (**Table 3**).

Hemorrhage and hypertensive disease development during pregnancy were same in both group and the rate of cesarean section was higher in control group even though it was not significant. While cesarean indications were fetal distress (50%), non-progressive labor and cephalopelvic disproportion in the epilepsy group, they were previous cesarean history (60%), fetal distress and cephalopelvic disproportion in the control group. There was no significant difference between groups in terms of fetal weight, fetal height, 1st and 5th minute Apgar scores while the prevalence rate of fetal malformation during delivery was significantly high in epilepsy group (**Table 3**).

Congenital malformation was observed in 5 (10.9%) newborns in the epileptic group, and in 4 (3.2%) newborns in the control group. There were 2 newborns with ventriculomegaly, 1 newborn with hydrocephaly, 1 newborn with cleft lip-palate, and 1 newborn with cardiac anomaly in the epilepsy group while there were 2 newborns with non-immune hydrops, 1 newborn with skeletal dysplasia and 1 newborn with gastroschisis in the control group. It was found out that the patients having babies with anomaly in the epileptic group did not receive folic acid replacement. Malformations observed in this group and the drugs they used are given in **Table 4.**

Discussion

Although the outcomes of more than 90% of epileptic and pregnant cases are good, an increase in maternal and fetal complications is observed in the epileptic pregnants compared to the society.[4] Increase

Table 3. Demographic and clinical data of the groups.

	Epilepsy group (46)	Control group (126)	p
Age (year)	**27.5±5.6**	**30±6.8**	**0.027**
Gravida	**2.52±1.55**	**3.61±2.54**	**<0.001**
Parity	**1.23±1.52**	**2.54±2.53**	**<0.001**
Abortus	**0.34±0.64**	**0.13±0.34**	**0.036**
Gestational week	36.56±2.51	36.42±2.69	0.758
Cesarean section	17 (37%)	60 (47.6%)	0.213
Fetal weight (g)	2965,86±821,9	3028,04±417,28	0.625
Fetal height (cm)	48.4±3.5	47.9±3	0.494
APGAR 1	6.1±1.2	6.2±1.5	0.528
APGAR 5	8.0±1.1	8.3±0.9	0.182
Anomaly (rate)	**5 (10.9%)**	**4 (3.2%)**	**0.045**

Table 4. Malformations detected and drugs used in the epilepsy group.

Malformations	Drugs used
Ventriculomegaly	Carbamazepine
Ventriculomegaly	Sodium valproate
Hydrocephaly	Oxcarbazepine + Sodium valproate
Cleft lip-palate	Carbamazepine + Sodium valproate
Cardiac anomaly	Carbamazepine + Sodium valproate

in epileptic seizures, AED use and maternal genes (that may be associated with epilepsy) are the most prominent potential factors for the occurrence of such complications.

The factor which has an apparent association with congenital malformations is the antiepileptic drugs used in the treatment. Epileptic seizures showing a one-third increase during pregnancy affects the health of mother and fetus negatively. It is considered that AED is significant for the increase of seizures since plasma concentrations decrease to sub-therapeutic levels due to low albumin concentration, increased body weight and total body fluid, and increased drug clearance during pregnancy. It was reported that drug levels are at sub-therapeutic levels in almost all of the epileptic pregnants who have an increase in seizure number.[5] Estrogen and progesterone levels increasing during pregnancy also may affect the occurrence and frequency of epileptic attacks.[6] Epileptic seizures frequently appears during the first trimester and it is considered that the condition is caused by interrupting treatment by pregnants in order to minimize the risks of AED on fetus. Özdemir et al. found out that 58.4% of 65 epileptic pregnants had epileptic attacks during their follow-up and these attacks were mostly during the first trimester.[7] In another study performed by Madazlı et al., it was reported that epileptic attacks were seen mostly during the first trimester.[8] In our study, it was observed that 39.1% of epileptic pregnants had seizure and 50% of them were during the first trimester. Antiepileptic drugs are one of the significant risk factors in epileptic patients. The risk for abortus, low birth weight, growth retardation in motor and mental functions, and congenital malformation is high in the babies of mothers using these drugs compared to those not using these drugs.[9,10] Nakane et al. found congenital malformation rate as 11.5% in those using AED and as 2.3% in those not using AED and reported five times higher increase. It was reported by Ergeneli et al. that anomaly rate in epileptic pregnants was 5.09 times higher than healthy pregnants.[11] In our study, congenital malformation was found in 10.9% of patients in the epileptic group and in 3.2% of patients in the control group. Although not as high as those published previously, anomaly rate in epileptic patients was found significantly higher than the control group. Congenital malformation risk increases in epileptic pregnants proportional to antiepileptic drug number used (polytherapy and monotherapy) and the increase in the dose. Therefore, it is recommended to use AED during pregnancy at the lowest dose to control seizures and as monotheraphy.[12,13] In our study, 3 of the pregnants found to have anomaly received polytherapy, 2 of them received monotheraphy consisting carbamazepine or sodium valproate, 4 of these patients had seizure at least once at the same time. Gestational category of classical AEDs used (carbamazepine, phenobarbital, phenytoin, valproic acid) is D in terms of their impacts; their fetal teratogenic effects are recognized, but they are used during pregnancy since their benefits are more than their harms.[14] There are studies showing that valproic acid and carbamazepine cause extremity anomalies (distal phalanx and nail hypoplasia), craniofacial anomalies (cleft lip-palate), and increase in congenital cardiac diseases.[15] On the other hand, it is considered that their effects on carbamazepine teratogenicity and fetal neurodevelopmental processes are lower than other antiepileptic drugs. Therefore, they are the antiepileptic drugs used during pregnancy frequently.[16] In our case, most of the patients had monotheraphy (67.4%) and carbamazepine was the most frequent one among them.

It is a necessary coenzyme required for the development of folates, erythrocytes and leucocytes. Dansky et al. found blood and erythrocyte folate level lower in women who delivered babies with anomaly compared to those who delivered healthy babies.[17] It is reported that neural tube defects are significantly high in women who did not receive preconceptional folate replacement, and using 4 mg folic acid before pregnancy decrease the occurrence of neural tube defect about 50%.[18] In our study, preconceptional 26 patients received folic acid replacement and ten patients began treatment after pregnancy was detected. While patients who were receiving the treatment of folic acid replacement delivered healthy babies, it was found out that none of the patients who delivered babies with anomaly did not use folic acid.

It is reported that weight of newborns of epileptic patients is lower than babies of healthy mothers. Hvas et al. found that newborn weight of epileptic pregnants

is 208 g lighter than newborns of control groups.[19] In our study, mean weight of newborns of epileptic pregnants is low compared to those in control group; however, there is statistically no significant difference between two groups. In the same way, the difference between newborns of two groups was not significant in terms of newborn height, and 1st and 5th minute Apgar scores.

Hiilesmaa and Viinkainen found no apparent difference in gestational complications of epileptic women, preeclampsia, preterm labor, and perinatal death rate.[20] Similarly, gestational complications were not found in none of the epileptic pregnants. Although vaginal delivery is recommended to epileptic pregnants, seizures that may develop due to stress and sleeplessness caused by delivery and uncertainty of complications that may be seen in labor management increase cesarean section rates in epileptic patients. Özdemir et al. reported cesarean rate as 66.2% in epileptic pregnants.[7] Hiilesma et al. found that there is an increase in operative delivery rate in this group. In our study, the cesarean rate was found as 56.5% in the epilepsy group and as 71.4% in the control group, and this difference was not statistically significant. It was found out that cesarean rate is high in the control group since 60% of the patients in this group had a previous cesarean history.

Conclusion

Consequently, epileptic pregnants have their unique risks. Preconceptional evaluation is quite significant for epileptic pregnants. These patients should be recommended to have the lowest dose of monotherapy and folate replacement treatment in their antiepileptic drug treatments. Epileptic patients should be followed-up closely and their treatments should be arranged from the moment they plan to become pregnant. The follow-up of these cases requires a team work consisting of experienced obstetricians, and if possible, perinatologists and neurologists. It is possible to obtain positive outcomes similar to general population by appropriate approach and follow-up.

Conflicts of Interest: No conflicts declared.

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