ORIGINAL RESEARCH

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Retrospective Evaluation of Pregnancy Outcomes with Maternal Epilepsy

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ABSTRACT Objective: To evaluate the clinical characteristics and obstetric outcomes of pregnant women with epilepsy at a tertiary center. **Material and Methods:** A total of 81 pregnant women with epilepsy were included in this retrospective cohort study. Clinical characteristics and obstetric outcomes were evaluated. **Results:** The mean maternal age of our cohort was 28.81±5.2 years, mean gravida was 1.78±1.17, mean gestational week at delivery was 37.8±2.07 , and mean birth weight was 2973±688.8 g with 4 (4.9%) preterm deliveries. Gestational diabetes mellitus was observed in 2 cases. Fetal growth restriction was detected in 3 (3.7%) cases. Ten neonates (12.3%) were admitted to the neonatal intensive care unit and no congenital chromosomal/structural anomalies were detected in any of the cases. Intrauterine fetal demise was observed in 1 (1.2%) case. The mean duration of epilepsy was 8.14 ± 5.8 years. Antiepileptic drugs were continued in 59 (72.8%) cases (11 polytherapy and 48 monotherapy). Six cases (7.4%) had seizures during pregnancy, and all 6 cases included patients who used medications during pregnancy. **Conclusion:** Favorable outcomes can be achieved in pregnant women with appropriately managed epilepsy.

Keywords: Carbamazepine; epilepsy; fetal; levetiracetam; neonatal; outcome; pregnancy; valproic acid

Epilepsy is the most common neurological disease encountered during pregnancy after migraine.[1] The prevalence of epilepsy in pregnant women has been estimated at 0.3-0.7%.[2,3] Progress in diagnosing and treating epilepsy has allowed many epileptic women to live a normal life and conceive a child.[4] Yet, there are fears of the potential adverse effects of antiepileptic drugs (AED) on the fetus and the varying frequency of seizures during pregnancy. Indeed, previous reports have documented an increase in the frequency of congenital anomalies following AED use.[1,3,5] Conversely, seizures during pregnancy confer a greater risk to both the mother and the fetus. Low birth weight, stillbirth, preterm delivery, fetal growth restriction (FGR), and increased risk of mental and psychomotor retardation in the offspring are the poor outcomes associated with these pregnancies.[6]

Therefore, epilepsy during pregnancy poses specific risks and an appropriate treatment, knowledge of the unique risks, and a coordinated treatment team is necessary to obtain favorable outcomes for both the mother and the fetus. In this study, we describe the clinical characteristics and obstetric outcomes of pregnant women with epilepsy at a tertiary center.

MATERIAL AND METHODS

A total of 81 pregnant women with epilepsy who delivered and had follow ups at the Division of Perinatology, Department of Obstetrics and Gynecology, Hacettepe University between 2007 and 2017 were evaluated in this retrospective cohort study. Data were obtained from Perinatology Division's computerized system. Patients who delivered at other healthcare facilities were excluded from the study.

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The diagnosis of epilepsy was made by expert neurologists. Maternal age, gravida, parity, type and duration of epilepsy, time interval between the last seizure and conception, antiepileptic drug use, and epilepsy status prior to pregnancy were reported. The presence of folic acid prophylaxis and the use of AED during pregnancy were determined. In addition, we evaluated whether patients changed their AED regimen and if they experienced episodes of epileptic seizures during pregnancy. Fetal congenital chromosomal/ structural anomalies, abortions, preterm deliveries, FGR, intrauterine fetal demise, neonatal death, and early neonatal complications were examined. Preterm delivery was defined as "delivery before 37 weeks of gestation" and FGR was defined as "less than the 10th percentile weight for the gestational age on a singleton growth curve". The mode of delivery, gestational age at birth, and birth weight were also evaluated.

Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS.22®, IBM SPSS, Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

The study protocol was approved by Hacettepe University Ethics Committee (GO 19/1064).

RESULTS

Clinical and demographic characteristics of the patients were given in Table 1. The mean maternal age was 28.81±5.2 years and mean gravida was 1.78 ±1.17. Three (3.7%) pregnancies were the result of in vitro fertilization. Gestational diabetes mellitus (GDM) was observed in only 2 (2.4%) patients, and 1 of them was receiving antiepileptic treatment (carbamazepine) during her pregnancy. No patients experienced chronic hypertension, gestational hypertension, preeclampsia/ eclampsia, amniotic fluid problems (polyhydramnios/oligohydramnios), or premature preterm rupture of membranes.

TABLE 1: Clinical and demographic characteristics of the patients.

Total (n)	**81 (100%)**
Maternal age (years)	28.81 ± 5.2
Gravida	1.78 ±1.17
Duration of epilepsy (years)	8.14 ± 5.8
The number of epileptic patients in the pre-pregnancy period	81 (100%)
Folic acid prophylaxis usage	81 (100%)
Antiepileptic drugs during pregnancy	
None	22 (27.2%)
Monotherapy	48 (59.2%)
Polytherapy	11 (13.6%)

Mean duration of epilepsy was 8.14±5.8 years. All of the patients were diagnosed with epilepsy before pregnancy and all of them used high dose (5 mg/day) folic acid supplement during 3 months before pregnancy.

The number of patients who continued epileptic treatment during pregnancy was 59 (72.8%). Twenty-two were not taking medication in the pre-pregnancy period with the decision of a neurologist. Other patients were not taking medication in the pre-pregnancy period with the decision of a neurologist. There were no patients who had drug changes or discontinued during pregnancy.

Polytherapy was administered in 11 (13.6%) cases and 48 (59.2%) patients received monotherapy. The distribution of patients receiving polytherapy was: oxcarbazepine and levetiracetam (n=4), valproic acid and lamotrigine (n=2), carbamazepine and valproic acid (n=2), levetiracetam and carbamazepine (n=1), levetiracetam and lamotrigine (n=1), and oxcarbazepine and valproic acid (n=1). Drug distribution in patients receiving monotherapy was: valproic acid (n=11), carbamazepine (n=15), oxcarbazepine (n=4), lamotrigine (n=7), phenytoin (n=1), and levetiracetam (n=10). Six patients (7.4%) had epileptic seizures despite AED usage [oxcarbazepine, (n=1), lamotrigine (n=2), carbamazepine (n=1), levetiracetam (n=1), and oxcarbazepine and levetiracetam (n=1)]. Six patients had seizures during pregnancy. Out of these 6 patients, 1 patient using lamotrigine had 4 seizures and the remaining 5 patients each had 1 seizure. Seizures were not observed in patients who did not receive AED treatment during pregnancy. Unfortunately, information on blood drug levels of the patients with seizures could not be obtained from the data system as the system had changed.

TABLE 2: Details of preterm births.

	GW at delivery	Neonatal birthweight	Mode of delivery	AED	Seizure during pregnancy	IUGR	NICU /days
Case 1	27.14	900.00	NSD		-	+	44
Case 2	32.28	1720.00	NSD	carbamazepin	-	-	5
Case 3	33.85	2000.00	CS		-	-	8
Case 4	33.85	2760.00	CS	carbamazepin	-	-	-

GW: Gestational weight, AED: Antiepileptic drugs, IUGR: Intrauterine growth restriction, NICU: Neonatal intensive care unit, NSD: Normal spontaneous delivery, CS: Cesarean section.

TABLE 3: Cases that needed NICU at the postnatal period.

	GW at delivery	Neonatal birthweight	Mode of delivery	AED	Seizure during pregnancy	IUGR	NICU /days
Case 1	27.14	900.00	NSD		-	+	44.00
Case 2	34.28	1380.00	CS	oxcarbamazepine	-	-	18.00
Case 3	34.71	1520.00	CS	carbamazepine	-	-	16.00
Case 4	33.85	2000.00	CS		-	-	8.00
Case 5	38.42	3170.00	CS	lamotrigine	-	-	8.00
Case 6	32.28	1720.00	NSD	carbamazepine	-	-	5.00
Case 7	37.28	2300.00	CS	carbamazepine. valproat	-	-	5.00
Case 8	37.28	2460.00	CS	carbamazepine. valproat	-	-	5.00
Case 9	37.28	3510.00	CS	lamotrigine	+(4 seizure)	-	4.00
Case 10	37.71	2900.00	CS	fenitoin	-	-	3.00

GW: Gestational weight, AED: Antiepileptic drugs, IUGR: Intrauterine growth restriction, NICU: Neonatal intensive care unit, NSD: Normal spontaneous delivery, CS: Cesarean section.

The mean gestational week at delivery was 37.8±2.07, and there were 4 preterm deliveries (4.9%) (Table 2). The mean birth weight was 2973 ± 688.8 g. FGR was detected in 3 (3.7%) cases. One of these patients was receiving oxcarbazepine and levetiracetam polytherapy, while the other 2 patients were not on any medication. The birth weight distribution of babies were: small for gestational age (SGA) (n=11), large for gestational age (LGA) (n=1), and appropriate for gestational age (AGA) (n=69). All mothers of SGA infants were taking AEDs [levetiracetam (n=3), carbamazepine (n=2), oxcarbazepine (n=1), oxcarbazepine and levetiracetam (n=1), carbamazepine and valproic acid (n=2), levetiracetam and lamotrigine (n=1), and levetiracetam and carbamazepine (n=1)]. The mother of the fetus who was LGA was receiving lamotrigine monotherapy.

Ten neonates (12.3%) were admitted to the neonatal intensive care unit (NICU) after delivery due to respiratory distress syndrome (n=9) and congenital pneumonia (n=1) (Table 3). Eight of the 10 mothers were taking AED during their pregnancies. All 10 neonates were discharged from the NICU without comorbidity. Intrauterine fetal demise was observed in 1 (1.2%) case that involved delivery by cesarean section (CS) at 37 weeks of gestation for repeated CS history. The baby was 3060 g and had no gross anomalies. Fetal autopsy could not be performed due to lack of parental approval and carbamazepine was used during the antenatal period. There were no cases of congenital chromosomal/structural anomalies in the study population.

DISCUSSION

Epilepsy is one of the most common chronic neurological conditions in the general population, with an estimated frequency of 0.6-1%. The approximate prevalence during pregnancy is 0.3-0.7%, with the number of pregnancies complicated by epilepsy in-

creasing over the previous decades due to advances in the fields of maternal-fetal medicine and neurology.[2-4] The main goals of physicians are to achieve favorable obstetric outcomes and to prevent seizures during pregnancy with minimal medication.[5] For this reason, appropriate preconception counseling is vital in order to plan the most appropriate drug treatment and to start folic acid supplementation as soon as possible.[5] However, approximately half of these pregnancies are unplanned.[5] In this study, we also aimed to report the results of pregnant women with epilepsy who were followed up in our center, and we have reflected that it is possible to achieve successful results with proper planning and follow-up.

Although there are still concerns on the safety of AEDs during pregnancy, preventing seizures with minimal medication is important to achieve favorable obstetric outcomes. Valproic acid should be avoided during pregnancy.[7] The relationship of valproic acid with congenital anomalies, SGA, and intrauterine growth restriction has been reported in many studies.[7-9] In our study, there were 11 patients who received valproic acid monotherapy without any complications. In addition, the following drug treatments were used in combination with valproic acid: 2 patients used lamotrigine, 2 patients used carbamazepine, 2 patients used levetiracetam, and 1 patient used oxcarbazepine. Only 2 of these patients had fetuses with SGA, and these 2 patients were receiving valproic acid plus carbamazepine polytherapy. Congenital anomalies and FGR were not observed in any of the newborns of the 18 women who received valproic acid treatment during pregnancy. Upon further exploration of the relationship between valproic acid and congenital anomalies, it was reported that babies with a congenital anomaly had higher levels of valproic acid in their blood, and the congenital anomalies may be due to the dose of valproic acid.[1] Unfortunately, in our study, the level of valproic acid in the blood of infants was unknown.

Previously, it was emphasized that AEDs were associated with SGA and FGR regardless of content and their effect on intrauterine fetal growth may have short and long term pediatric outcomes.[6] Of the 3 infants with FGR in our study, 2 of the mothers did not use AEDs, while the remaining mother was taking oxcarbazepine and levetiracetam polytherapy.

The only intrauterine fetal demise incidence in our study was with a mother who used carbamazepine during her pregnancy. There are no statements that AEDs are associated with intrauterine fetal death, therefore, we think this is an independent and random situation.

In addition to growth restriction, the requirement for use in the NICU is another parameter to consider with maternal AED use. In a study on this subject, no association was found between maternal epilepsy and NICU administration.[1] In our study, only 10 babies needed postnatal NICU admission, mostly due to neonatal respiratory problems.

Another reported obstetric outcome of maternal AED use is preterm delivery.[4] A population-based comprehensive study reported that the frequency of preterm labor was increased in women using AED for any reason other than epilepsy, and emphasized that preterm labor was associated with AED rather than epilepsy.[6] In our series, there were 4 preterm labors. Two of these patients did not use AEDs, the other 2 patients were using carbamazepine. Today, levetiracetam and lamotrigine are the first choice when an AED is needed during pregnancy as they are considered safer than the other AEDs.[5] However, there are disadvantages to these agents, such as requiring frequent follow-ups since blood levels may change during pregnancy, and when control levels cannot be achieved, epileptic seizures may occur.[5] Previously, the seizure-free rate of pregnant women was reported to be approximately 30.88%.[4] In our series, only 6 patients (7.4%) had seizures during pregnancy. One patient used oxcarbazepine, 2 used lamotrigine, 1 used carbamazepine and levetiracetam, and 1 used oxcarbazepine and levetiracetam. The patient who was using lamotrigine had 4 seizures during her pregnancy and each of the other 5 patients each had only one seizure. Seizures were not observed in patients who did not receive AED during pregnancy. We believe that the strict and multidisciplinary follow-up of the patients in our series led to this low seizure rate. In addition to treatment and follow-up, other issues that needed to be

addressed in these patients were increased perinatal morbidity and mortality.

Complications ranged from mild to severe and included preeclampsia, preterm labor, bleeding, placental abruption, poor fetal growth, prematurity, fetal death, and maternal mortality.[10-12] The increased risk has been reported to be quite low for these complications. The increase in risk for maternal mortality is less than 0.1 percent. There are a number of possible explanations for this finding, including an increase in medical comorbidities among women with epilepsy, an increase in life-threatening complications of pregnancy, and an increase in seizure-related complications, including sudden unexpected death in epilepsy.[12,13] There were no cases of maternal deaths in our series.

The mechanism of increased risk of fetal death among pregnant women with epilepsy is also not well understood. In a previous study, only 1 of 165 reported miscarriages or stillbirths was associated with seizures or status epilepticus; two-thirds of these pregnancies were seizure-free.[14] Another study showed that the risk of stillbirth was paradoxically increased in high-income countries.[15,16] We experienced only one intrauterine fetal demise in our series, and there was no history of seizure during pregnancy under carbamazepine treatment.

In another study, it was reported that AED exposure is associated with an increased risk of preterm birth and the effect was also present among women who were prescribed AEDs for a psychiatric indication, suggesting the effect may be medication associated.[17] Our mean gestational week at delivery was 37.8 (range: 27.14- 41.42) weeks, with 4 preterm births. We did not observe an increased rate of preterm deliveries compared to the low risk population in our study.

In addition to fetal death, stillbirth, and preterm birth, women with epilepsy have a small but significant increased risk for a number of additional perinatal outcomes. In a large study, cesarean delivery (41 versus 33 percent), pregnancy-related hypertension (10.5 versus 7.9 percent), preeclampsia (6.7 versus 4.2 percent), antepartum hemorrhage [2.1 versus 1.5 percent), postpartum hemorrhage (including severe postpartum hemorrhage (0.7 versus 0.4 percent)], preterm labor (11 versus 7 percent), and poor fetal growth (3.7 versus 2.1 percent) were moderately higher among women with epilepsy compared with women without epilepsy.[12] We did not experience these complications in our study probably due to the limited number of cases.

We had only 2 patients with GDM, and to our knowledge, there are no reports in the literature regarding the relationship between epilepsy and GDM or AED usage during pregnancy.

Women with epilepsy suffer from this disease throughout their life and need frequent and regular follow-ups. With the desire to have children during reproductive age, clinical care for these women becomes more complex. However, in recent years, seizure-free periods have increased with advancements in drug alternatives, providing comfortable prenatal and postnatal care for women with epilepsy, similar to low risk patients. Although AEDs should be selectively applied during pregnancy with regular and strict follow-ups, a seizure-free pregnancy has become increasingly probable in these patients.

CONCLUSION

In conclusion, strict and regular follow-ups and clinical care should be performed in multidisciplinary centers to monitor AED use in pregnant women diagnosed with epilepsy. When these pregnancies are managed professionally in this way, these women can be provided maximum comfort during pregnancy with an increase in good obstetric outcomes.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members

of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet Sinan Beksaç;* ***Design:*** *Mehmet Sinan Beksaç, Emine Aydın;* ***Control/Supervision:*** *Mehmet Sinan Beksaç;* ***Data Collection and/or Processing:*** *Emine Aydın;* ***Analysis and/or Interpretation:*** *Emine Aydın;* ***Literature Review:*** *Emine Aydın;* ***Writing the Article:*** *Emine Aydın, Mehmet Sinan Beksaç;* ***Critical Review:*** *Mehmet Sinan Beksaç;* ***References and Fundings:*** *Emine Aydın, Mehmet Sinan Beksaç;* ***Materials:*** *Emine Aydın, Mehmet Sinan Beksaç.*

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