Pregnancy outcome of 149 pregnancies in women with epilepsy: Experience from a tertiary care hospital

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Abstract: Introduction: Epilepsy has a prevalence of 1.65% in adults, and every 1 in 200 pregnancies encounters its complications. We aimed to present the existing condition of and our experience with epileptic pregnant women for whom the prepregnancy counseling is inadequate in Turkey. Methods: We evaluated 149 epileptic pregnant women between March 2009 and January 2015. Demographic features of the patients, along with type and duration of epileptic seizure, time of diagnosis, date of last seizure prior to pregnancy, number and duration of seizures during pregnancy, type of AEDs, result and week of termination of pregnancy, and birth weight were registered, and also, we evaluated perinatal complications and fetal malformations. Results: Mean age of the patients was 27.12 ± 5.4 years, and mean duration from the diagnosis of epilepsy to pregnancy was 9.68 ± 5.91 years. Twenty-seven (18.12%) and 101 (67.78%) patients had polytherapy and monotherapy, respectively. We observed epileptic seizures in 103 (69.12%) patients during pregnancy, and seizures mostly occurred in the first and third trimesters. Forty-one (39.80%) patients had seizures in all three trimesters. Forty-two (28.18%) patients among all patients who had seizures during pregnancy had 5 or more seizures. Major malformations, namely, cleft lip and palate, ventriculoseptal defect, and spina bifida were observed in the patients. Mean birth week was 38.43 ± 1.68 weeks, and mean birth weight was 2965.31 ± 453.94 grams. Twenty-two patients had normal spontaneous vaginal delivery whereas 118 patients had cesarean section. Conclusions: Pregnant women with epilepsy have their own risks. These women should be followed by experienced obstetricians and neurologists during their pregnancies. Appropriate management and follow-up lead to good results almost the same as general population.

Keywords: epilepsy, pregnancy, seizures, antiepileptic drugs

Introduction

Epilepsy has a prevalence of 1.65% in adults, and every 1 in 200 pregnancies encounters its complications. Following headaches, epilepsy is the second most common, but the most serious neurological condition in pregnant women. Although both progesterone and estrogen have been shown to influence the activity of seizures, the relationship between this activity and pregnancy has been unclear. During pregnancy, 46% of epileptic women have stable seizure frequency; however, 20% and 34% of women experience a decrease and an increase in seizure activity, respectively [1].

It has been widely believed that epileptic women are at greater risk of seizures during pregnancy. However, studies in the English literature report different complication rates with no clear data. Although more than 90% of pregnant women do not encounter complications related to epilepsy, it has been reported that complications increase to some degree, and dismal obstetric outcome may be observed. Hence, prepregnancy counseling for epileptic women and careful management of both the pregnancy period and the delivery are of high importance [2].

Furthermore, a vast number of anticonvulsant medications should be investigated for their teratogenic effects. It was stated that newborns exposed to antiepileptic drugs (AEDs) in utero have 2–3-fold higher (3.3–9%) prevalence of major congenital abnormalities compared to that of none exposed newborns [3].

Congenital malformations such as cleft lip and palate, cardiac defects, neural tube defects (NTDs), skel-
et al abnormalities, and hypospadias have been shown to occur as a result of intrauterine exposure to AEDs. These malformations are observed more frequently with increased doses of AEDs, higher serum levels of AEDs and polytherapeutic approaches [4]. Folic acid may also be responsible for the occurrence of major complications to some degree as folic acid supplementation in women under anticonvulsant medications has been shown to decrease malformation rates [5].

Epileptic women are under higher risks of abortion and premature delivery, and the newborn may encounter low birth weight, developmental delay, and even increased rate of fetal and neonatal death. Maternal deaths are also increased 10-folds in epileptic women mostly owing to quitting or noncompliance to medications leading to increased frequency of seizures [6].

Management of epileptic seizures during pregnancy includes decreasing the maternal and fetal risks due to uncontrolled seizures together with minimizing the potential teratogenic effects of AEDs. Guidelines recommend to (a) choose the optimal treatment before conception, (b) prefer monotherapy approach if possible, (c) opt for the most efficient AED according to the type and frequency of seizures, (d) begin with the lowest effective dose, and (e) not forget folic acid supplementation [7].

In our study, we aimed to present the existing condition of and our experience with epileptic pregnant women for whom the prepregnancy counseling is inadequate in Turkey. Also, we intended to investigate the controversial subjects with regard to our data, and we reviewed the current approaches for epileptic pregnancy cases in the light of current data.

Methods

We evaluated 149 epileptic pregnant women who were followed in Ankara Numune Training and Research Hospital, Department of Gynecology and Obstetrics between March 2009 and January 2015. The patients had been diagnosed with epilepsy either in the neurology department of our hospital or by other neurologists in other health institutions. We excluded the patients whose diagnosis was not made by specialists of neurology or who had a history of suspicious epileptic seizures long years ago.

We registered demographic features of the patients such as age, gravida, and parity along with type and duration of epileptic seizure, time of diagnosis, date of last seizure prior to pregnancy, number and duration of seizures during pregnancy, type of AEDs, result and week of termination of pregnancy, birth weight, and perinatal complications. We evaluated fetal malformations, abortion, preterm birth, intrauterine growth retardation (IUGR), and early neonatal problems. We also investigated if prepregnancy counseling was taken, folic acid prophylaxis was performed, or they continued using AEDs during pregnancy. All patients were consulted every other month to neurology clinic starting from the date they learned out their pregnancy.

Ethics

Written informed consent was obtained from the patient for publication of this case report. The article does not violate the policies and/or procedures established by journal such as those described in “Specific Inappropriate Acts in Publication Process”.

Results

Mean age of the patients was 27.12 ± 5.4 years (17–41 years), and mean duration from the diagnosis of epilepsy to pregnancy was 9.68 ± 5.91 years (1–28 years). Twenty-five (16.78%) patients had focalized seizures whereas 124 (83.22%) patients had generalized epilepsy. In patients with generalized epilepsy, 105 (84.68%) had tonic–clonic, 15 (12.09%) had myoclonic, and 4 (3.23%) had absence seizures (Table I). All cases were diagnosed with symptomatic epilepsy by a neurologist.

Sixty-two (41.61%) of all 149 patients had applied to our clinic with pregnancy plans and were consulted to neurology. Among these patients, 23 patients had been using valproic acid previously, and it was replaced by another AED in all patients. Antiepileptic drug dose was decreased in 28 patients whereas, in 6 patients, AED was stopped as they had been without seizures for a long time. A hundred-one and 27 patients had monotherapy and polytherapy, respectively. Sixteen patients stopped using AEDs gratuitously and 21 patients in total, together with 5 patients whose medication was stopped prior to pregnancy, were followed without medication (Table II). Folic acid replacement therapy was given preconceptionally to all patients planning pregnancy, and it was started at the time that pregnancy had been learned in unplanned pregnancies.

Forty-six (30.88%) patients did not have seizures during pregnancy. Eleven (23.91%) of these patients were not on medication whereas 31 (67.39%) and 4 (8.70%) patients were on monotherapy and polytherapy, respectively. We observed epileptic seizures in 103 (69.12%) patients during pregnancy, and seizures mostly occurred in the first and third trimesters. Twenty-six (25.24%), 2 (1.94%), and 22 (21.36%) patients had seizures in the only first, only second, and only third trimesters, respectively. Forty-one (39.80%) patients had seizures in all three trimesters. Forty-two (28.18%) patients among all patients who had seizures during pregnancy had 5 or more seizures.
### Table I  Demographic criteria of included epileptic pregnant women

| Demographic Criteria                                      | Value                          |
|-----------------------------------------------------------|-------------------------------|
| Age (years)                                               | 27.12 ± 5.4                   |
| Duration of epilepsy (years)                             | 9.68 ± 5.91                   |
| Gestational age at delivery (weeks)                       | 38.43 ± 1.68                  |
| Fetal birth weight (grams)                                | 2965.31 ± 453.94              |
| Type of epileptic seizure                                 |                               |
| - Focalized seizure                                       | 25 (16.78)                    |
| - Generalized seizure                                     | 124 (83.22)                   |
| | a. Tonic-clonic                                          | 105 (84.68)                   |
| | b. Myoclonic                                             | 15 (12.09)                    |
| | c. Absence                                               | 4 (3.23)                      |
| Type of AEDs                                               |                               |
| - No treatment                                            | 21 (14.10)                    |
| - Monotherapy                                             | 101 (67.78)                   |
| - Polytherapy                                             | 27 (18.12)                    |
| Delivery                                                  |                               |
| - Spontaneous abortion                                    | 7 (4.70)                      |
| - Dilation & curettage                                    | 2 (1.34)                      |
| - Vaginal route                                            | 22 (14.76)                    |
| - Cesarean section                                        | 118 (79.20)                   |
| Seizures during pregnancy                                 |                               |
| - No seizures                                             | 46 (30.87)                    |
| - Seizures                                                | 103 (69.13)                   |
| | a. 1 seizure                                             | 22 (14.36)                    |
| | b. 2 seizures                                            | 13 (12.62)                    |
| | c. 3 seizures                                            | 21 (20.39)                    |
| | d. 4 seizures                                            | 3 (2.91)                      |
| | e. 5 or more seizures                                    | 42 (40.78)                    |
| | f. Status epilepticus                                    | 2 (1.94)                      |
| | **Fetal malformations**                                  |                               |
| | a. Cleft lip and palate                                  | 1 (0.67)                      |
| | b. Ventricleseptal defect                                | 1 (0.67)                      |
| | c. Spina bifida                                          | 1 (0.67)                      |
| | **Perinatal complications**                              |                               |
| | a. IUGR                                                  | 20 (13.42%)                   |
| | b. Preterm labor                                          | 8 (5.36%)                     |
| | c. Preeclampsia                                           | 1 (0.67%)                     |
| | **Last seizure prior to pregnancy**                      |                               |
| | a. Last >5 years                                         | 8 (17.40)                     |
| | b. Last 3–5 years                                        | 10 (21.73)                    |
| | c. Last 1–3 years                                        | 18 (39.13)                    |
| | d. Last 3–12 months                                      | 8 (17.40)                     |
| | e. Last 3 months                                         | 2 (1.34)                      |
| | **Seizures during pregnancy groups**                     |                               |
| | a. Last >5 years                                         | 1 (0.97)                      |
| | b. Last 3–5 years                                        | 2 (1.94)                      |
| | c. Last 1–3 years                                        | 20 (19.41)                    |
| | d. Last 3–12 months                                      | 6 (5.83)                      |
| | e. Last 3 months                                         | 74 (71.85)                    |

**Abbreviations:** AEDs, antiepileptic drugs; IUGR, intrauterine growth retardation.

*Values are given as mean ± SD

### Table II  Distribution of cases antiepileptic drugs (AEDs) using and seizures during pregnancy

| AEDs n (%) | Seizures during pregnancy n (%) |
|------------|---------------------------------|
| No treatment | 21 (14.10) | 10 (6.71) |
| Monotherapy n (%) | 101 (67.78) | 70 (46.97) |
| - Carbamazepine | 41 (27.52) | 26 (17.45) |
| - Lamotrigine | 20 (13.42) | 14 (9.40) |
| - Valproic acid | 19 (12.75) | 15 (10.06) |
| - Levatiracetam | 13 (8.72) | 10 (6.71) |
| - Oxcarbazepine | 8 (5.37) | 5 (3.35) |
| Polytherapy | 27 (18.12) | 23 (15.43) |
| - Levatiracetam + carbamazepine | 17 (11.41) | 13 (8.72) |
| - Valproic acid + lamotrigine | 8 (5.37) | 8 (5.37) |
| - Levatiracetam + valproic acid | 2 (1.34) | 2 (1.34) |

**Abbreviations:** AEDs, antiepileptic drugs
Status epilepticus developed in 2 patients with 8- and 9-week-old pregnancies, and pregnancies were terminated by dilation and curettage (D&C). Both patients had had diagnosis of epilepsy for more than 5 years, had had seizures in the last month prior to pregnancy, and were on carbamazepine and levatiracetam polytherapy.

Fourty-six out of 36 patients who had no seizures during pregnancy had also had no seizures during the last 1 year prior to pregnancy. Seventy-four out of 103 patients who had at least one seizure during pregnancy had a history of epileptic seizures in the last 3 months prior to pregnancy. All patients with 5 or more seizures during pregnancy had a history of seizures in the last 1 year prior to pregnancy, and 37 of them had also had seizures in the last 3 months.

Seven patients who had epileptic seizures in the first weeks of pregnancy had spontaneous abortion, and all were unplanned pregnancies. Major malformations, namely, cleft lip and palate, ventricularseptal defect, and spina bifida were observed in these patients, and they were on carbamazepine monotherapy, levatiracetam and carbamazepine polytherapy, and lamotrigine and valproic acid polytherapy, respectively.

IUGR and preterm labor were observed in 18 and 8 patients, respectively. Fifty percent of patients with IUGR, and all patients with preterm labor had seizures in the third trimester. One patient who stopped medication gratuitously and had seizures in all trimesters developed preeclampsia in the 36th week.

Mean birth week was 38.43 ± 1.68 weeks (30–41 weeks), and mean birth weight was 2965.31 ± 453.94 grams (1700–4240 grams). Twenty-two patients had normal spontaneous vaginal delivery whereas 118 patients had cesarean section (C-section). Among patients who had C-section delivery, 39 (38.05%) patients were operated according to neurologist advice due to frequent seizures, 45 (38.13%) patients had previous C-sections, 32 (27.12%) patients had suspicious traces of heart beats, and 2 (1.70%) patients had malpresentation. One patient who had had frequent seizures during pregnancy had generalized tonic-clonic seizure following normal spontaneous vaginal delivery; however, no additional seizures were observed. No seizures occurred in the early postpartum period in patients who had C-section delivery.

Conclusions

Increased number of seizures and increased risk of fetal malformations are the major concerns in pregnant women with epilepsy. Although earlier studies reported that seizures deteriorate during pregnancy, this is not the case at the present time owing to better prenatal follow-up. In a recent community-based prospective study, epilepsy was stated to be either better controlled or proceeded stable in 83% of pregnant women [8]. Meadow et al. [7] found the seizure-free rate 81% in 333 pregnant women in a multicentered study. Similarly, we did not detect any alterations in the frequency of seizures in 79% of 149 pregnant women with epilepsy in our study. In case of an increase in the frequency of seizures, it usually occurs during the first trimester and generally returns to the baseline at the pregestational period when the pregnancy terminates. However, seizure control has been reported to worsen in a number of patients. In our study, 26% of the patients have seizures in the only first trimester whereas 41% of them were affected in all three trimesters.

Seizure control in the preconception period is also crucial. Controlling the seizures gets harder during pregnancy in the majority of patients with a history of frequent seizures (i.e., more than once in a month) in the prepregnancy period; however, increase in the frequency of seizures during pregnancy occurs in approximately 25% of patients with a history of fewer attacks (i.e., less than once in every 9 months) in the prepregnancy period. Vajda and colleagues reported a 50–70% decrease in the risk of having seizures during pregnancy in patients with no seizures in the previous year [9]. We observed that 78.26% of the patients without seizures during their pregnancy period had had no seizures in the previous 1 year. However, all 42 patients who had at least 5 seizures during pregnancy had had a history of at least one seizure in the last year before conception.

Increase in the frequency of seizures is generally a result of subtherapeutic levels of anticonvulsants or a lower threshold of seizures, or both. A number of pregnant women discontinue using anticonvulsants owing to their concerns on teratogenic effects of these drugs. The increased metabolic capacity of the maternal liver and the possible effect of fetal or placental metabolism may affect the anticonvulsant drug requirement in epileptic women during pregnancy [9].

Status epilepticus may occur in pregnancy period without any preceding increase in the frequency of seizures, occasionally due to the injudicious discontinuation of anticonvulants. Although this condition is rare, it may lead to a fatal outcome for the mother or the fetus. The absence of hypertension, proteinuria, and edema helps the clinician to distinguish this condition from an eclamptic seizure. As in nonpregnant patients, it is essential to control the seizures as soon as possible, but the former practice of terminating pregnancy has widely been abandoned [10]. We observed status epilepticus in two women who were 8 and 9 weeks pregnant following epileptic seizures in their first trimesters, and pregnancies were terminated by dilation and curettage (D&C). Both patients had diagnosis of epilepsy for more than 5 years, had had seizures in the last month prior to pregnancy, and were on carbamazepine and levetiracetam polytherapy during pregnancy.
Recent evidence suggests that untreated epilepsy does not lead to increased malformations in the fetus [11]. However, the fetus of an epileptic mother taking anticonvulsant medication has an indisputably increased risk of congenital malformations. It is now clearly known that all antiepileptic drugs can cross the placenta, and therefore, they are all potentially teratogenic. Mono- therapeutic antiepileptic use causes fewer birth defects compared to politherapy. Furthermore, increasing the monotherapy dose is still superior to adding another agent regarding fetal complications [12]. Monotherapy with phenytoin, carbamazepine, and presumably phenobarbital has been observed to increase the rate of major malformations by two or three times compared to general population [13]. Lamotrigine may have a similar risk. Distinctively, the effects of valproate on fetal complication rate are dose-dependent, and the risk may increase to as high as eightfold [13]. It was also shown that valproate monotherapy has negative effects on cognitive function around age 3 [14].

In regard to polytherapy, the risk is increased with each additional drug. The most frequently reported defects are orofacial clefts, cardiac malformations, and neural tube defects. For instance, orofacial clefts are encountered approximately tenfold more frequently compared to the general population. Specialized ultrasonography may help to identify these possible anomalies in the midpregnant period. In our study, 78.9% and 21.1% of patients who used antiepileptic medication during pregnancy were on monotherapy and polytherapy, respectively. The most commonly used drug in patients on monotherapy was carbamazepine. Spontaneous abortion occurred in 7 patients who had had epileptic seizures in the early weeks of pregnancy, and these pregnancies were all unplanned. We observed three major malformations, namely, cleft lip and palate, ventriculoseptal defect, and spina bifida, and the mothers were using carbamazepine monotherapy, levetiracetam and carbamazepine poly- therapy, and lamotrigine and valproic acid polytherapy, respectively.

Epileptic women are also on slightly increased risk of certain pregnancy complications other than seizures [15]. In a Swedish study of 1207 epileptic women, Pilo and colleagues reported a 1.5-fold increase in the incidence of cesarean delivery, preeclampsia, and postpartum hemorrhage [16]. Postpartum depression was also shown to be increased in these women [17]. Whether preterm labor is encountered more frequently in epileptic women is not clear. Stillbirth rates are significantly higher among epileptic women; however, epilepsy has not been clearly shown to be associated with increased rate of low birthweight. In our study, we observed IUGR in 20 cases, and preterm labor in 8 cases. Sixty percent of cases with IUGR, and all cases with preterm labor had had seizures during the third trimester. Preeclampsia developed in the 36th week of pregnancy in a patient who had stopped taking medications injudiciously, and had had seizures in all three trimesters.

Women with epilepsy may benefit from preconceptional counseling. They should be informed about the optimal management of anticonvulsant therapy. Mono- therapy with the least teratogenic drug should be the treatment of choice, or if this is not possible, the number of drugs should be minimized. Folic acid supplementation is likely to decrease the rate of malformations in women who are using anticonvulsants [3]. In our study, 59.73% of the patients had planned pregnancies and had started to take folic acid supplementation prior to conception. In the rest of the patients with unplanned pregnancies, folic acid use started after the diagnosis of pregnancy.

The major aim of treatment in epileptic women is to prevent seizures. In order to accomplish this goal, nausea and vomiting, if present, should be treated, stimuli that are likely to provoke seizures should be avoided, and medication should strictly be complied. Anticonvulsant dose should be at its lowest level that can control seizures. Although some clinicians prefer to closely follow up the serum levels of antiepileptic drugs during pregnancy, altered protein binding may make this control unreliable. Furthermore, there is no evidence that such monitoring improves seizure control [18]. Besides, in spite that it may be helpful, measurement of free or unbound drug levels is not widely available.

Cesarean section is not essentially performed in all pregnant women with epilepsy. However, it is indicated in patients with frequent seizures, patients having seizures during labor, patients who are not able to cooperate during labor due to any reason such as neurologic or mental disorder, and patients in whom seizures are provoked by physical activity [19]. In our study, 22 (14.76%) women had normal spontaneous vaginal, and 118 (79.20%) had cesarean delivery. The causes for cesarean section were neurologist’s recommendation due to frequent seizures during pregnancy in 33.05%, history of cesarean delivery in 38.13%, unstable heart beat trace in 27.12%, and malpresentation in 1.7% of the patients.

Fetal death can result from maternal seizures, presumably because of the accompanying hypoxia and acidosis. The effect on placental blood flow of maternal seizures is not established, but changes in fetal heart rate suggestive of hypoxia have been described; they may relate to reduced placental blood flow or to metabolic changes in the mother [20]. An increased incidence of neonatal death has been reported for the offspring of epileptic mothers. The increased rate may relate to several factors, including congenital malformations, iatrogenic neonatal hemorrhage, seizures, socioeconomic issues, and preterm delivery. Recently, we reported the effects of history of seizures during pregnancy on umbilical arterial blood gas values in pregnant women with epilepsy and we found when patients with a history of 5 or more
epileptic seizures during pregnancy were compared with the control group without epilepsy and the patients with epilepsy who had no history of seizures during pregnancy, there was no statistically significant difference although their umbilical arterial blood pH values were found to be lower while partial carbon dioxide pressure (pCO₂) values were higher and partial oxygen pressure (pO₂) values were lower [21].

The main goal in the follow-up of pregnant women with epilepsy is to control the seizures with the possibly lowest medication dose. In order to reach this goal, the efficient drug dose should be assessed prior to pregnancy. Triggering factors such as insomnia and stress should be eliminated, and continuation of AED use should be provided during pregnancy. In women with epilepsy who plan to get pregnant, 4 mg of prophylactic folic acid should be recommended by preconceptional counseling. Pregnancy follow-up should be performed with great care particularly in terms of congenital anomalies, and these patients should be evaluated with ultrasonography by experienced clinicians. The act of labor is particularly risky for epileptic seizures, and special caution should be performed together with keeping the pregnant women away from stress, insomnia, and starvation. As a result, pregnant women with epilepsy have their own risks. These women should be followed by experienced obstetricians and neurologists during their pregnancies. Appropriate management and follow-up lead to good results almost the same as general population.

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