

# Self-Discontinuation of Antiseizure Medication During Pregnancy Increases Postpartum Seizure Frequency

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## ABSTRACT

**Objectives:** The study aimed to investigate the rate of unplanned pregnancies, changes in seizure frequencies during the 6 months before the pregnancy, during the pregnancy, and the 6 months after the pregnancy, and antiseizure medication (ASM) compliances in women with epilepsy (WWEs).

**Materials and Methods:** The study retrospectively evaluated WWEs who were followed up in the epilepsy outpatient clinic of a training and research hospital between 1997-2021 and had used ASMs for at least 6 months prior to their pregnancy.

**Results:** The study assessed a total of 158 pregnancies for 77 WWEs, with 112 pregnancies resulting in live births, 71.4% of which were unplanned pregnancies. Unplanned pregnancies are more common in less educated women ( $p = 0.02$ ). Of the women, 35 self-discontinued their ASMs during pregnancy, and these women were younger than the WWEs who continued taking their ASMs ( $p = 0.003$ ). In addition, folic acid supplement use was lower in women who self-discontinued their ASMs ( $p = 0.031$ ). The rate of increase in seizure frequency during postpartum period compared to pregnancy was higher in women who self-discontinued ASMs ( $p = 0.032$ ).

**Conclusion:** Self-discontinuation of ASM during pregnancy is related to an increase in postpartum seizure frequency. WWEs should be given advice on how to minimize the risk of seizure during the postpartum period.

**Keywords:** Epilepsy, pregnancy, seizures, postpartum period

## INTRODUCTION

Epilepsy is a common neurological disease affecting 0.3% to 0.6% of pregnant women (1, 2). Managing pregnancy for women with epilepsy (WWEs) is challenging in terms of both the mother's and child's health. Antiseizure medications (ASMs) increase the risk of congenital defects, intrauterine growth retardation, miscarriage, stillbirth, and preterm birth in WWEs, and recent reports have also mentioned the negative impact of ASMs on children's mental functions (3–6). This is concerning for the physician as well as for mothers with epilepsy and their family.

Despite the well-known adverse effects of ASMs, pregnant WWEs may be required to continue their medications to protect both themselves and the fetus from seizures that may occur during pregnancy. Even though dose reduction may be possible if the seizures are under control, WWEs should be advised to have been free of seizures for at least 1 year before the pregnancy (7, 8). Furthermore, due to sleep deprivation and postpartum depression, the postpartum period is hazardous for seizure recurrence (9). Preconception counseling is important for WWEs to minimize adverse events and have a complication-free pregnancy (3). However, studies have also indicated

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unplanned pregnancy rates to range from 16.2%-60.6% (10-12). With unplanned pregnancies in general, WWEs abruptly discontinue their ASMs or reduce their dosage once they find out they are pregnant due to the anxiety of the teratogenic effects of ASMs. Noncompliance with ASMs during pregnancy is reported to be around 20% in the literature (13). For these reasons, managing the pregnancy of WWEs can be challenging.

This study aimed to investigate the rate of unplanned pregnancies, changes in seizure frequencies during the 6 months before the pregnancy, during the pregnancy, and the 6 months after the pregnancy, ASM compliances, and pregnancy outcomes for WWEs.

## MATERIALS AND METHODS

This study retrospectively evaluated female patients who'd been seeking treatment in an epilepsy outpatient clinic of a training and research hospital between January 1997-November 2021. The study involves women who'd been diagnosed with epilepsy prior to a pregnancy and who had used ASMs for at least 6 months prior to their pregnancy.

The study retrieved its data from patient files that include their demographic characteristics, education level, type of epileptic seizures, seizure frequency (before, during, and after pregnancy), whether the pregnancy was planned or not, and the use of folic acid supplements. The types of epileptic seizures have been defined according to the International League Against Epilepsy (ILAE) 2017 classification using electroencephalography (EEG) findings along with seizure history, and ASM adherence was monitored through patients' statements. The unplanned pregnancy group consists of WWEs who experienced unexpected pregnancies and who consulted an epileptologist post-conception. With regard to planned pregnancies, 5 mg of folate supplementation was started three months before the planned conception. With regard to the unplanned pregnancies, however, folic acid supplementation was introduced in the first follow-up visit following the start of the pregnancy. Follow-up visits were done in 3-month intervals.

Seizure frequency was evaluated over three periods: the 6 months before the pregnancy (T1), during the pregnancy (T2), and the 6 months after the pregnancy (T3). Changes in seizure frequency between each of these three periods was assessed and classified under three categories: Unchanged, increased, or decreased. Pregnancies that resulted in a miscarriage, stillbirth, medical abortion, or curettage have been excluded from the comparison regarding seizure frequency. More than a 50% increase in seizure frequency during and after a pregnancy compared to before is considered as increased seizure frequency, while a more than 50% decrease is considered as decreased seizure frequency.

Pregnancy outcomes have been grouped in terms of live births, spontaneous miscarriages, medical abortions, curettage, stillbirths, and ectopic pregnancies. Stillbirths are defined as pregnancies that result in fetal death after the 23<sup>rd</sup> week of

pregnancy.

Antiseizure medications used during pregnancy and their doses have been noted for all pregnancies. Seizure frequencies have been compared between WWEs who self-discontinued ASMs and those who maintained their treatment.

These retrospectively collected data have been anonymized. Therefore, no need exists for written consent. This study was approved by a Haseki Training and Research Hospital Institutional Review Board committee (approval number: 2021-273).

## Statistical Analyses

Statistical analyses have been performed using the program SPSS 21.0 for Windows. Descriptive statistics are presented as numbers and percentages for categorical variables and as means, standard deviations, minimums, and maxima for numeric variables. The chi-square test is used to compare two independent groups, while the numeric variables in two independent groups are compared using Student's t test when normality is not met. For more than two independent groups, numeric variables are compared using the one-way ANOVA test when normally distributed and using the Kruskal-Wallis test when normality is not. McNemar's test has been preferred for comparing percentages of independent groups, and subgroup analyses have been interpreted using the Bonferroni correction. All *p* values are two-sided with a statistical significance of 0.05.

## RESULTS

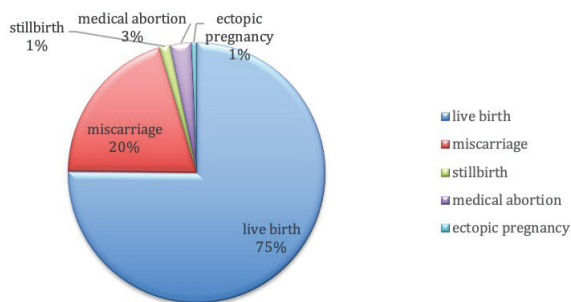
The demographic and clinical characteristics of the patients included in the study are summarized in Table 1. The outcomes of the pregnancies are shown in Figure 1. Among the 30 miscarriages, 18 pregnancies involved mothers undergoing monotherapy, five involve mothers undergoing polytherapy, and seven involved mothers who'd self-discontinued their ASM. Among the four medical abortions, one pregnancy was terminated because the fetus had anencephaly and the mother was taking 750 mg/day of valproic acid (VPA), one fetus had unknown developmental problems and the mother was taking 600 mg/day of carbamazepine (CBZ), one fetus had hydronephrosis and the mother was taking 400 mg/day of CBZ, and one pregnancy was terminated because the mother had severe seizures while taking 600 mg/day of CBZ and 50 mg/day of lamotrigine (LTG).

The characteristics of the 112 pregnancies that resulted in a live birth are presented in Table 2. Of these live births, 35 women had self-discontinued their ASMs, 14 of whom restarted upon seizure recurrence. The remaining 21 pregnancies (plus another two who'd stopped their ASMs under the close care of their physician for a total of 23 pregnancies) went to term without medications. Reduced ASM dosage occurred in 23 pregnancies in an attempt to lessen the teratogenesis risk, while the ASM dosage was increased in four pregnancies in order to improve seizure control.

**Table 1.** Demographical and clinical characteristics of women with epilepsy.

	N=77	
<b>Age at epilepsy onset (year) (mean±sd)</b>	14.13±0.62	
<b>Age at presentation (year) (mean±sd)</b>	23.69±0.77	
<b>Age at first pregnancy (year) (mean±sd)</b>	23.08±0.47	
<b>Follow-up duration (year) (mean±sd)</b>	8.50±0.63	
<b>Number of pregnancies (mean±sd)</b>	2.58±0.21	
	<b>N</b>	<b>%</b>
<b>Consanguineous marriage</b>	14	18.2
<b>Number of years of education</b>		
≤8 years	61	79.2
≥8 years	16	20.8
<b>Type of epileptic seizures*</b>		
Focal	26	33.8
Generalized	51	66.2
<b>Number of pregnancies</b>		
1	22	28.6
2	24	31.2
3	16	20.8
≥4	6	19.5

\* There were 26 patients with focal (6 structural/lesional, 19 with unknown causes) and 51 patients (5 juvenile absence epilepsy (JAE), 27 juvenile myoclonic epilepsy (JME), 19 others) with generalized seizures



**Figure 1.** Outcomes of pregnancies.

The rate of planned pregnancies was observed to be 28.6%. No association was found between planned/unplanned pregnancies with change in seizure frequency or ASM use before pregnancy (e.g., monotherapy/polytherapy;  $p > 0.05$ ). The mean age at conception and mean duration of disease were significantly higher with regard to planned pregnancies ( $p = 0.013$  and  $p = 0.049$ , respectively). Planned pregnancies were more common for women who'd received eight or more years of education and women experiencing their first pregnancies ( $p = 0.034$  and  $p = 0.011$ , respectively; Table 3).

**Table 2.** Characteristics of pregnancies with live births.

	N=112	%
<b>Route of delivery</b>		
Vaginal route	69	61.6
Cesarean section	43	38.4
<b>Planned pregnancy</b>	32	28.6
<b>Folic acid use</b>	78	69.6
<b>Treatment discontinuation</b>	35	31.3
<b>ASM use during pregnancy</b>		
No ASMs	23	20.5
Monotherapy	68	60.7
Polytherapy	21	18.8

ASM: Antiseizure medication

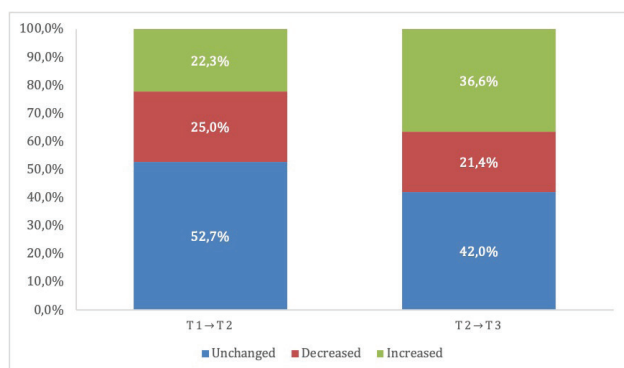
The changes in seizure frequency between T1 and T2 differ significantly from the changes in seizure frequency between T2 and T3 ( $p = 0.000$ ). Between T2 and T3, the rates for unchanged

**Table 3.** Pregnancy planning and associated factors.

		Pregnancy planning		P-value
		Planned N=32 N(%)	Unplanned N=80 N(%)	
<b>ASM use before pregnancy</b>	Monotherapy	26 (81.3)	60 (75.0)	.645
	Polytherapy	6 (18.8)	20 (25.0)	
<b>Number of years of education</b>	≤8 years	11 (34.4)	47 (58.8)	<b>.034</b>
	≥8 years	21 (65.6)	33 (41.3)	
<b>First pregnancy</b>	Yes	22 (68.8)	32 (40.0)	<b>.011</b>
	No	10 (31.3)	48 (60.0)	
<b>Mean age at conception (year) (mean±sd)*</b>		28.19±4.96	25.54±4.91	<b>.013</b>
<b>Mean duration of disease (year) (mean±sd)*</b>		13.56±5.94	11.06±7.07	<b>.049</b>
Change in seizure frequency during pregnancy compared to preconceptional period	Unchanged	16 (50.0)	43 (53.8)	.904
	Decreased	8 (25.0)	20 (25.0)	
	Increased	8 (25.0)	17 (21.3)	
Change in seizure frequency during postpartum period compared to pregnancy	Unchanged	14 (43.8)	33 (41.3)	.951
	Decreased	7(21.9)	17 (21.3)	
	Increased	(34.4)	30 (37.5)	
	No	28(80.0)	52(65.0)	

ASM: Antiseizure medication  
 \*Mann Whitney U test

and decreased seizure frequencies declined while the rates for increased seizures grew compared to the respective frequency changes from T1 to T2 (Figure 2). Furthermore, an increase in seizure frequency was observed between T2 and T3 in 65.2% of pregnancies where the women were being monitored without ASM ( $p = 0.008$ ). No association was found between the change in seizure frequency between T2 and T3 with regard to the type of epileptic seizure, duration of disease, or age at conception ( $p > 0.05$ ; Table 4).



**Figure 2.** Change in seizure frequencies.  
 T1→T2: Comparison between T1 and T2  
 T2→T3: Comparison between T2 and T3

The results for noncompliance with antiepileptic treatment during pregnancy are presented in Table 5. The mean age of women who'd discontinued ASMs during pregnancy was significantly lower ( $p = 0.002$ ). The use of folic acid supplementation was also significantly associated with drug discontinuation, with 75.6% of patients who used folic acid supplements continuing their ASMs, while 47.1% of patients who did not take folic acid discontinued their ASMs ( $p = 0.031$ ). Noncompliance with ASM therapy was higher in patients who'd received eight years or less of education or who were in their first pregnancies, although the difference was not statistically significant ( $p = 0.333$  and  $p = 0.284$ , respectively). No significant association was found between ASM self-discontinuation and change in seizure frequency between T1 and T2 ( $p = 0.702$ ). However, the rate of increase in seizure frequency between T2 to T3 was higher in women who'd discontinued their ASM while pregnant ( $p = 0.032$ ).

## DISCUSSION

This study has evaluated the pregnancies of 77 WWEs undergoing treatment in an epilepsy outpatient clinic whose rate of unplanned pregnancies was observed to be 71.4%. The ratio of planned pregnancies has been shown to vary according to countries' development levels, with unplanned pregnancies being reported at 16.2% in the Natsal-3 study in Britain (10), 46.2% in Japan (11), and 60.6% in China

**Table 4.** Change in seizure frequency during postpartum period compared to pregnancy and associated factors.

		Change in seizure frequency during postpartum period compared to pregnancy			P-value
		Unchanged N=47 N(%)	Decreased N=24 N(%)	Increased N=41 N(%)	
<b>ASM use during pregnancy</b>	No ASMs	6 (12.8)	2 (8.3)	15 (36.6)	<b>.008</b>
	Monotherapy	34 (72.3)	14 (58.3)	20 (48.8)	
	Polytherapy	7 (14.9)	8 (33.3)	6 (14.6)	
<b>Type of epileptic seizures</b>	Focal	16 (34.0)	12 (50.0)	9 (22.0)	.067
	Generalized	31 (66.0)	12 (50.0)	32 (78.0)	
<b>Mean age at conception (year) (mean±sd)*</b>		26.94±5.37	26.00±4.91	25.73±4.78	.513
<b>Mean duration of disease (year) (mean±sd)*</b>		11.89±6.72	10.58±6.34	12.34±7.31	.603

ASM: Antiseizure medication  
\*One way ANOVA test

**Table 5.** Noncompliance with antiepileptic treatment and associated factors.

		Drug discontinuation		P-value
		Yes N=35 N(%)	No N=77 N(%)	
<b>Pregnancy planning</b>	Planned	7(20.0)	25(32.5)	.259
	Unplanned	28(80.0)	52(67.5)	
<b>ASM use before pregnancy</b>	Monotherapy	27 (77.1)	59 (76.6)	.952
	Polytherapy	8 (22.9)	18 (23.4)	
<b>Folic acid use</b>	Yes	19 (54.3)	59 (76.6)	<b>.031</b>
	No	16 (45.7)	18 (23.4)	
<b>Number of years of education</b>	≤8 years	21 (60.0)	37 (48.1)	.333
	≥8 years	14 (40.0)	40 (51.9)	
<b>First pregnancy</b>	Yes	20 (57.1)	34 (44.2)	.284
	No	15 (42.9)	43 (55.8)	
<b>Mean age at conception (year) (mean±sd)*</b>		24.23±4.82	27.23±4.89	<b>.002</b>
<b>Mean duration of disease (year) (mean±sd)*</b>		10.20±6.98	12.49±6.69	.108
Change in seizure frequency during pregnancy compared to preconceptional period	Unchanged	20 (57.1)	39 (50.6)	.702
	Decreased	7 (20.0)	21 (27.3)	
	Increased	8 (22.9)	17 (22.1)	
Change in seizure frequency during postpartum period compared to pregnancy	Unchanged	11 (31.4)	36 (46.8)	<b>.032</b>
	Decreased	5 (14.3)	19 (24.7)	
	Increased	19 (54.3)	(28.6)	

ASM: Antiseizure medication  
\*Mann Whitney U test

(12). Data from the Pregnancy Risk Assessment Monitoring System (PRAMS) reported 55% of pregnancies for WWEs to be unplanned (15), while data from the Epilepsy Birth Control Registry (EBCR) reported this rate to be 65% (16). The rate of planned pregnancies among WWEs in Turkiye has been found to range from 28.6%-41.6% (17, 18). According to data from field research conducted on the general population in Turkiye, 26% of pregnancies are unplanned. Similar to the current study, unexpected pregnancies are lower in women who have at least eight years of education and for first pregnancies (19). WWEs noteworthy have a high rate of unplanned pregnancies despite having a chronic disease.

The rate of ASM self-discontinuation was found to be 31.3%. Noncompliance with ASM during pregnancy among the WWEs has been reported to vary between 15%-62.3% in the literature (1, 13). According to Turkish studies, this rate ranges between 10.7%-25% (18, 20). Pregnant WWEs are twice as likely to stop ASM as nonpregnant WWEs (21). The current study discovered WWEs who'd self-discontinued their ASMs had a lower mean age. This finding is consistent with the findings from Sweileh et al. (22). Women who don't use folic acid supplements were also found to have higher rates of ASM self-discontinuation in the current study. Similarly, one study (23) investigating adherence to medication among pregnant women with chronic diseases found women who do not use folic acid supplementation to have a higher risk of non-compliance with their treatment. Fear of the teratogenic consequences of ASMs was the main reason in this study for WWEs' poor adherence. A lack of folate supplements further increased the risk of congenital abnormalities. Therefore, negative beliefs about ASMs and self-discontinuation could be lessened through proper counseling during the preconception period and by ensuring the use of folic acid supplementation.

The postpartum period saw a greater increase in seizure frequency. Moreover, the current study demonstrated the increase in seizure frequency to be higher in pregnancies of women who were monitored while not taking medication during pregnancy. Vajda et al. (24) noted obtaining seizure control both before and during pregnancy to increase the chance of remaining seizure-free during the postpartum period. Although a comparison of seizure frequencies during the preconception and postpartum periods has not been thoroughly explored, postpartum sleep deprivation, exhaustion, and increased stress may increase the risk of seizure in WWEs (9, 25). Therefore, it was recommended to keep the dose of ASM higher than in the preconceptional period (9). Different life modifications should also be made during this period. Sleep deprivation is inevitable, especially for breastfeeding mothers. WWEs should be advised to take precautions such as sharing burden of nighttime feeding with other people and attempting to make up for the lack of sleep during the infant's daytime naps (26, 27).

As this study involves a records-based search, it is subject to the accompanying limitations involving restricted details

about the patient population and the potential of missing or misinterpreting data. The information in the study is based on the reliability of the patient's self-recall without the use of seizure diaries. The small sample size and lack of a control group are other limitations of the study. Additionally, the characteristics of pregnancies with and without live births could not be compared.

The current research reveals a significantly greater rate of unplanned pregnancies to have occurred among WWEs, as well as a high rate of ASM self-discontinuation. In a survey study, it was found that for 87% of the WWEs that considered having children, the potential effect of epilepsy and ASMs on the unborn child was their most crucial concern. Furthermore, this study also emphasizes preconception counseling to have been inadequate, so much so that 33% of the WWEs hadn't even received any information about their pregnancy and epilepsy medication (28). For this reason, negative beliefs about ASMs should be lessened through proper counseling during the preconception period. Finally, postpartum seizure frequency was seen to have increased more significantly for WWEs who'd self-discontinued their ASMs. WWEs should be provided counseling on how to minimize the risk of having a seizure during the postpartum period. This includes emphasizing the significance of drug adherence as well as proper sleep with the help of another person.

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**Ethics Committee Approval:** This study was approved by the Haseki Training and Research Hospital Institutional Review Board committee (approval number: 2021-273).

**Peer-review:** Externally peer-reviewed.

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