ORIGINAL ARTICLE

Changes in Seizure Frequency and Antiepileptic Therapy during Pregnancy

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ABSTRACT

BACKGROUND

Among women with epilepsy, studies regarding changes in seizure frequency during pregnancy have been limited by the lack of an appropriate nonpregnant comparator group to provide data on the natural course of seizure frequency in both groups.

METHODS

In this prospective, observational, multicenter cohort study, we compared the frequency of seizures during pregnancy through the peripartum period (the first 6 weeks after birth) (epoch 1) with the frequency during the postpartum period (the following 7.5 months after pregnancy) (epoch 2). Nonpregnant women with epilepsy were enrolled as controls and had similar follow-up during an 18-month period. The primary outcome was the percentage of women who had a higher frequency of seizures that impaired awareness during epoch 1 than during epoch 2. We also compared changes in the doses of antiepileptic drugs that were administered in the two groups during the first 9 months of epoch 1.

RESULTS

We enrolled 351 pregnant women and 109 controls with epilepsy. Among the 299 pregnant women and 93 controls who had a history of seizures that impaired awareness and who had available data for the two epochs, seizure frequency was higher during epoch 1 than during epoch 2 in 70 pregnant women (23%) and in 23 controls (25%) (odds ratio, 0.93; 95% confidence interval [CI], 0.54 to 1.60). During pregnancy, the dose of an antiepileptic drug was changed at least once in 74% of pregnant women and in 31% of controls (odds ratio, 6.36; 95% CI, 3.82 to 10.59).

CONCLUSIONS

Among women with epilepsy, the percentage who had a higher incidence of seizures during pregnancy than during the postpartum period was similar to that in women who were not pregnant during the corresponding epochs. Changes in doses of antiepileptic drugs occurred more frequently in pregnant women than in nonpregnant women during similar time periods. (Funded by the National Institutes of Health; MONEAD ClinicalTrials.gov number, NCT01730170.)

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The treatment of women with epilepsy during pregnancy requires a balance between maintaining stable control of maternal seizures and the potential adverse effects of some antiepileptic drugs on the developing fetus. Convulsive seizures are dangerous to both the mother and fetus as a result of blunt trauma and hypoxemia.[1] Several studies have reported a higher incidence of maternal death among pregnant women with epilepsy than among other pregnant women, with up to 79% of epilepsy-related deaths attributed to sudden, unexpected death.[2-4] Ranges of an increased frequency of seizures during pregnancy have varied from 14 to 62%.[5-9] The practice guidelines of the American Academy of Neurology concluded there is insufficient evidence to determine whether the changes in seizure frequency are related to pregnancy itself, because studies have not included an appropriate nonpregnant comparator group to provide data on the natural course of seizure frequency in both groups of women with epilepsy.[10]

We conducted the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study to evaluate six goals regarding women with epilepsy during pregnancy and outcomes in their infants. The first of these goals was to determine whether women with epilepsy have a higher frequency of seizures during pregnancy than when they are not pregnant. Here, as part of achieving the first goal, we report the results of a study involving women with epilepsy to determine whether the percentage who had a higher frequency of seizures during pregnancy than they did during the postpartum period was greater than the percentage of nonpregnant women during the same time period. We also compared changes in the dose of antiepileptic drugs among pregnant women and nonpregnant women and assessed the risk factors for an increased seizure frequency during pregnancy.

Methods

Study Design

This ongoing prospective, observational, parallel-group study is being conducted at 20 epilepsy centers in the United States that have a specialty focus on the treatment of women with epilepsy.[11] Included in the study are pregnant women with epilepsy and a control cohort of nonpregnant women with epilepsy between the ages of 14 and 45 years. Exclusion criteria for the two groups include an expectation that the patient would have a hard-to-measure or substantially altered frequency of seizures (e.g., the presence of progressive cerebral disease, planned surgical intervention for epilepsy, a history of psychogenic nonepileptic seizures, or drug or alcohol abuse in the previous year) or features that were expected to alter other primary outcomes of the study (e.g., >20 weeks of gestation in the pregnant group, an intelligence quotient of less than 70, or a change in the dose of an antiepileptic drug that occurred before enrollment during pregnancy or in the 90 days before enrollment in the control group). Additional details regarding the inclusion and exclusion criteria are available in the protocol, available with the full text of this article at NEJM.org.

The study was approved by the institutional review board at each study site. From December 2012 through January 2016, we recruited women by distributing brochures, posting flyers at health centers, sending letters to referring physicians, and distributing business cards during clinical visits. Most of the women in the two study groups were patients of the epilepsy clinics at the study sites. The antiepileptic-drug treatment was determined by each woman's clinical team throughout the study. All the women provided written informed consent.

Study Evaluations

We conducted study visits for the pregnant women three times during pregnancy, during hospitalization for labor and delivery, and every 3 months through 9 months during the postpartum period (total evaluation period, 18 months). Women in the control group participated in the same number of visits as the pregnant women. Gestational age was calculated on the basis of the estimated due date, and the first study visit could be scheduled up to 20 weeks of gestation to enhance recruitment. Visits during the second and third trimesters were scheduled between 21 and 27 weeks and between 30 and 36 weeks, respectively. When the first visit occurred within the second trimester, the next visit was separated by at least 4 weeks.

The control group was composed of women who had characteristics that were similar to

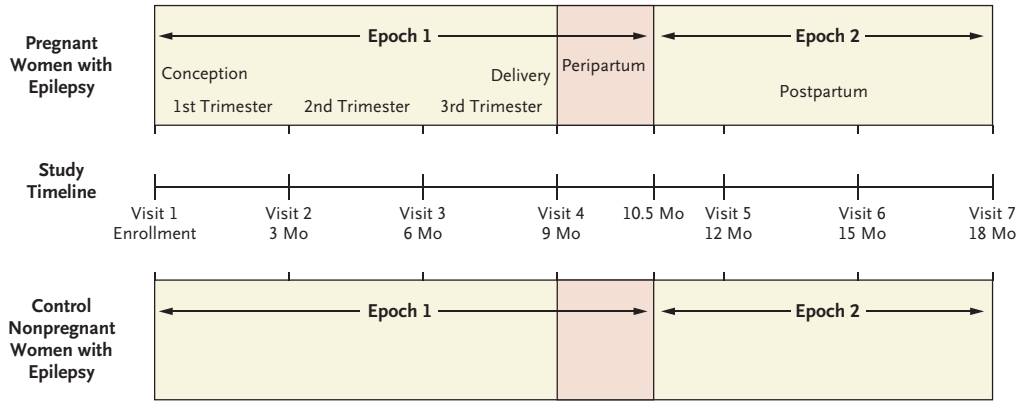

Figure 1. Study Design.

Among both pregnant and nonpregnant (control) women who were enrolled in the study, the primary outcome was determined by the incidence of seizures that impaired awareness during epoch 1 as compared with epoch 2. Among pregnant women, enrollment (visit 1) occurred at a gestational age of 20 weeks or less. Visits during the second and third trimesters were scheduled between 21 and 27 weeks and between 30 and 36 weeks, respectively. When the first visit occurred within the second trimester, the next visit was separated by at least 4 weeks.

those of the pregnant women with respect to age, educational status, race, seizure type, seizure frequency, seizure-freedom rate, drug category (monotherapy vs. polytherapy), and type of antiepileptic drug received. After 20% of women had been recruited, the members of the study executive team performed a weekly review of the characteristics of the women in the two groups to ensure balance on the basis of these factors. An enrollment restriction was enacted in July 2013 when an imbalance was detected, with closure of enrollment to nonpregnant women in the control group who were receiving antiepileptic-drug polytherapy.

The main comparisons in the study required the definition of two epochs. Among the pregnant women, epoch 1 included pregnancy (enrollment date through delivery) and the peripartum period, which was defined as the 6 weeks after birth (total, 10.5 months). We combined the peripartum period with pregnancy because studies have suggested that the period within the first 6 weeks after birth may be associated with an increased risk of seizures.[12] Epoch 2 included the period from 6 weeks to 9 months after birth (total, 7.5 months). For women in the control group, epoch 1 began at the time of enrollment and extended through the following 10.5 months, and epoch 2 included the following 7.5 months (Fig. 1).

At the first study visit, we collected data regarding the demographic characteristics of the women, along with a general medical history and detailed epilepsy history, including the age of onset, seizure type, history of epilepsy risk factors, and previous results on imaging and electroencephalography. Site investigators classified seizures and epilepsy syndromes using the criteria of the National Institute of Neurological Disorders and Stroke.[13] Members of the epilepsy classification core committee validated the types of seizures and forms of epilepsy in each woman.

The study participants used an electronic-diary smartphone application (www.irody.com) to submit daily information regarding the type and frequency of seizures, the type and dose of medication, and their adherence to the drug regimen. Site coordinators reviewed the electronic-diary entries with the participants at study visits, verified changes in drug type or dose, and entered any missing electronic-diary entries into a seizure log.

Outcomes

The primary outcome was the percentage of women who had a higher frequency of seizures that impaired awareness during epoch 1 than during epoch 2. The percentages of women with this outcome were then compared in the two groups. Although all seizure types were investi-

gated, seizures that impaired awareness were selected as the primary outcome because of their potential for adverse clinical consequences. The frequency of seizures was normalized to a 28-day rate for time periods that were analyzed (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

Secondary outcomes were the percentage of women who had an increased frequency of seizures in each trimester and in the peripartum period, the percentage who had an increased frequency of other seizure types, the percentage who had a change in the dose of antiepileptic drugs during pregnancy, the within-person change in the 28-day incidence of seizures, and the percentage of women who had seizures or convulsions during epoch 1 among those who were seizure-free or convulsion-free during the 9 months before pregnancy or enrollment. Among the pregnant women, we also evaluated risk factors for an increased frequency of seizures during epoch 1 as compared with epoch 2. For this evaluation, we selected four risk factors of interest: freedom from seizures during the 9 months before pregnancy or enrollment, seizure type, medication category (monotherapy vs. polytherapy), and medication category plus drug group (lamotrigine monotherapy, levetiracetam monotherapy, polytherapy with levetiracetam plus lamotrigine, and other monotherapy or polytherapy).

STATISTICAL ANALYSIS

We determined that the enrollment of 350 pregnant women and 100 controls would provide a power of more than 85% to detect a between-group difference of 15 to 20 percentage points in the percentage of women who had an increased frequency of seizures (the primary outcome), assuming a frequency of 10 to 20% in the control group and a 15% dropout rate.

We calculated the percentage of women who had an increased frequency of seizures (along with 95% confidence intervals) in epoch 1 as compared with epoch 2 to summarize the results of all outcomes, including the primary outcome. We calculated odds ratios and 95% confidence intervals from logistic-regression models for each seizure type for between-group comparisons. We summarized continuous outcomes such as within-person changes in 28-day frequency of seizures by calculating means and 95% confidence intervals along with medians and ranges as a post hoc secondary outcome. To minimize extreme values in the 28-day frequency of seizures owing to missing electronic-diary records, we considered that data were missing for a particular trimester or analysis time period (i.e., epoch 1) if coordinators were unable to verify at least 30 days of data regarding seizures for a participant within that time period (Fig. S1).

For each seizure type or category (e.g., seizures with impaired awareness), the analysis included only the women who had reported a history of having that seizure type at enrollment. The subgroups of the overall analysis population were selected in this manner to avoid inflating the number of women who reported having no change in the frequency of seizures who would not have been susceptible to a particular type of seizure. Changes in the type or dose of antiepileptic drugs during pregnancy are reported in a manner that was similar to the methods used to report changes in seizure outcomes.

Risk factors associated with seizure worsening during epoch 1 were evaluated with the use of logistic-regression models. Unadjusted models were fitted for each prespecified risk factor, and an adjusted model was fitted to include risk factors and covariates that were chosen through a forward selection procedure.

Covariates that were considered in adjusted models included the baseline maternal age, education, race, ethnic group, IQ (as evaluated on the Peabody Picture Vocabulary Test, fourth edition[14]), a history of a catamenial pattern of seizures,[15] and lifetime history of depression (as assessed by an instrument for a structured clinical interview for depression).[16] Because there was no prespecified plan for adjustment of confidence intervals for the outcomes, no definite conclusions can be drawn from these data, and the results are given as point estimates and 95% confidence intervals that have not been adjusted for multiple comparisons.

Post hoc sensitivity analyses were performed to evaluate the robustness of the primary-outcome results. These analyses addressed between-group differences in the frequency of seizures during epoch 2, the choice of postpartum or prepregnancy as the comparator state among nonpregnant women, and the use of multiple imputation to assess the effect of missing data. A summary of the sensitivity analyses is provided in the Supplementary Appendix. All the analyses

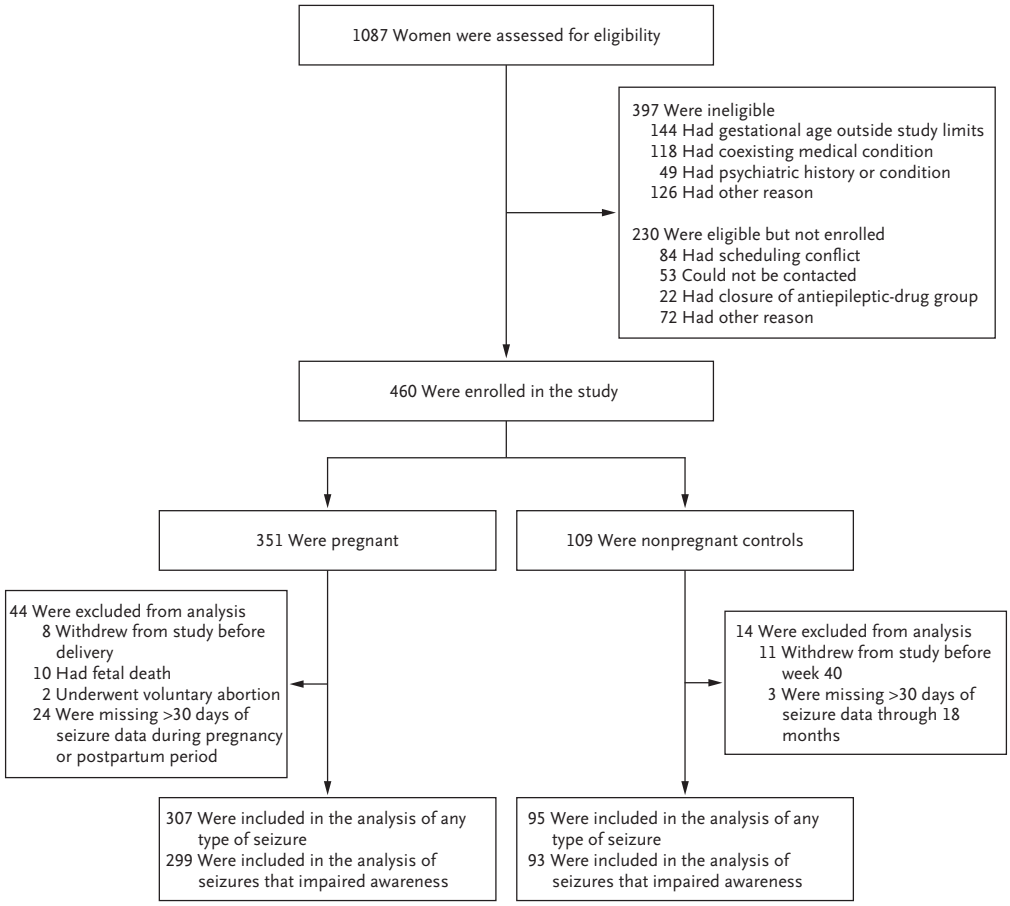

Figure 2. Enrollment and Outcomes.

Study participants could have more than one reason for lack of eligibility or nonenrollment. In the two groups, among the reasons for withdrawal from the study were scheduling conflicts, transportation issues, pregnancy in the control group, and loss to follow-up.

were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

A total of 1087 women were assessed for eligibility, which resulted in the enrollment of 351 pregnant women and 109 controls (Fig. 2). A total of 299 of 351 pregnant women (85%) and 93 of 109 controls (85%) were included in the main analysis of seizures that impaired awareness; 87% of the women in the two groups (307 and 95, respectively) were included in the analysis of any seizure type. Pregnant women and controls were similar in terms of demographic features, seizure types, types of antiepileptic drugs that were used, and the percentages who were seizure-free during the 9 months before pregnancy or enrollment (Table 1).

PRIMARY AND KEY SECONDARY OUTCOMES

The primary outcome (a frequency of seizures that impaired awareness that was higher in epoch 1 than in epoch 2) occurred in 70 of 299 pregnant women (23%) and in 23 of 93 controls (25%) (odds ratio, 0.93; 95% confidence interval [CI], 0.54 to 1.60) (Table 2, Fig. 3A, and Table S1). Among the key secondary outcomes, the distribution of the increase in seizure frequency

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Pregnant Women (N=307)	Controls (N=95)
Age — yr	31±5	30±7
Education — no. (%)		
No college degree	87 (28)	24 (25)
College or advanced degree	220 (72)	71 (75)
IQ	98±13	102±11
Race — no. (%)†		
White	262 (85)	88 (93)
Black	19 (6)	3 (3)
Other	26 (8)	4 (4)
Seizure type — no. (%)‡		
Generalized	95 (31)	29 (31)
Focal	189 (62)	57 (60)
Unclassified	26 (8)	10 (11)
Seizure-free during 9-mo period before pregnancy or enrollment — no./total no. (%)	158/306 (52)	45/95 (47)
Antiepileptic-drug monotherapy — no. (%)		
Any	235 (77)	77 (81)
Lamotrigine	101 (33)	30 (32)
Levetiracetam	88 (29)	30 (32)
Carbamazepine	13 (4)	3 (3)
Oxcarbazepine	12 (4)	3 (3)
Zonisamide	11 (4)	4 (4)
Other§	10 (3)	7 (7)
Antiepileptic-drug polytherapy — no. (%)		
Any	58 (19)	18 (19)
Lamotrigine plus levetiracetam	24 (8)	6 (6)
Other§	34 (11)	12 (13)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQ denotes intelligence quotient.
† Race was reported by the participants.
‡ Participants could report more than one seizure type. Four women reported having multiple seizure types: generalized and focal seizures in two pregnant women and one control and generalized and unclassified seizures in one pregnant woman.
§ Three pregnant women and two controls were receiving valproate as either monotherapy or polytherapy. Other drugs included topiramate, lacosamide, felbamate, gabapentin, phenobarbital, phenytoin, clonazepam, lorazepam, ethosuximide, pregabalin, and perampanel.

in epoch 1 as compared with epoch 2 was similar in the two groups within trimesters and according to seizure type (Table 2 and Fig. S2). The distribution of baseline characteristics was similar in the two groups of women who were included in an analysis of each seizure type (Table S5). During epoch 1, at least one seizure that impaired awareness was reported in 87 of 299 pregnant women (29%) and in 29 of 93 controls (31%); during epoch 2, at least one such seizure was reported in 78 of 299 pregnant women (26%) and in 14 of 93 controls (15%) (Table S2).

OTHER SECONDARY OUTCOMES

The mean frequency of seizures that impaired awareness, as normalized to a 28-day value and measured as a continuous outcome, was 0.69 seizures in epoch 1 and 0.55 seizures in epoch 2

Table 2. Primary and Secondary Outcomes.*

Outcome	Pregnant Women		Controls		Odds Ratio (95% CI)†
	no. of women	*no. with outcome (%)*	*no. of women*	*no. with outcome (%)*	
Primary outcome					
Higher frequency of seizures that impaired awareness during epoch 1 than during epoch 2‡	299	70 (23)	93	23 (25)	0.93 (0.54–1.60)
Secondary outcomes					
Primary outcome, according to timing					
First trimester (wk 0–13)	41	3 (7)	92	14 (15)	0.44 (0.12–1.62)
Second trimester (wk 14–28)	290	44 (15)	92	16 (17)	0.85 (0.45–1.59)
Third trimester or delivery (wk 29+)	273	40 (15)	90	11 (12)	1.23 (0.60–2.52)
Peripartum (delivery to 6 wk after birth)	275	34 (12)	88	7 (8)	1.63 (0.70–3.83)
Primary outcome, according to seizure type§					
Any type	307	110 (36)	95	32 (34)	1.10 (0.68–1.79)
Convulsive	269	39 (14)	82	12 (15)	0.99 (0.49–1.99)
Focal	189	73 (39)	57	20 (35)	1.16 (0.63–2.16)
Generalized	95	29 (31)	29	8 (28)	1.15 (0.46–2.91)
Unclassified	26	8 (31)	10	4 (40)	0.67 (0.15–3.03)
≥1 change in dose of antiepileptic drug in women with a history of seizures that impair awareness¶	299	222 (74)	93	29 (31)	6.36 (3.82–10.59)

* Included in the primary and secondary analyses were study participants for whom valid seizure data were available for at least 30 days during both epoch 1 (pregnancy and peripartum period or the first 10.5 months for controls) or the specified pregnancy stage and epoch 2 (postpartum period or 7.5 months after epoch 1 for controls).
† The odds ratios and 95% confidence intervals (CIs) were calculated with the use of a logistic-regression model. Because there was no adjustment for multiple comparisons, no inferences can be drawn from the confidence intervals for the secondary outcomes.
‡ Seizures that impaired awareness included all absence seizure subtypes, generalized tonic–clonic seizures, clonic seizures, tonic seizures, atonic seizures, focal seizures with impairment of consciousness or responsiveness, focal evolving to bilateral tonic–clonic convulsions, and unclassified seizures with impairment of consciousness or responsiveness.
§ The sample size for each seizure type represents the number of study participants who had a history of that seizure type at enrollment.
¶ This analysis was conducted in pregnant women at the time of delivery and in controls at 9 months after enrollment.

among pregnant women and 1.40 and 0.28 seizures, respectively, among nonpregnant women (Table S1). The frequency of seizures was higher in epoch 1 than in epoch 2 among both pregnant women and controls, with a mean change of 0.14 seizures per 28 days (95% CI, −0.04 to 0.31) and 1.12 seizures per 28 days (95% CI, −1.05 to 3.28), respectively (Table S3). Among the women who were seizure-free or convulsion-free during the 9 months before pregnancy or enrollment, no between-group difference was observed in the percentage of women who had seizures or convulsions during epoch 1 (Table S6).

Among the women with seizures that impaired awareness, at least one change in the dose of an antiepileptic drug was reported in 222 of 299 pregnant women (74%) by the time of delivery and in 29 of 93 controls (31%) by 9 months after enrollment (odds ratio, 6.36; 95% CI, 3.82 to 10.59) (Table 2 and Fig. 3B). In 209 of 299 pregnant women (70%), the dose of an antiepileptic drug was higher by the end of pregnancy than in the period before pregnancy, as compared with an increase in 22 of 93 controls (24%) during the corresponding period (odds ratio, 7.49; 95% CI, 4.37 to 12.84) (Table S7). Figure S3 shows the changes in doses of the six most common antiepileptic drugs according to trimester and postpartum period.

In risk-factor models for calculating a higher frequency of seizures in epoch 1 than in epoch 2, the odds ratio for being seizure-free during the 9 months before pregnancy or enrollment was 0.22 (95% CI, 0.12 to 0.41). Models were

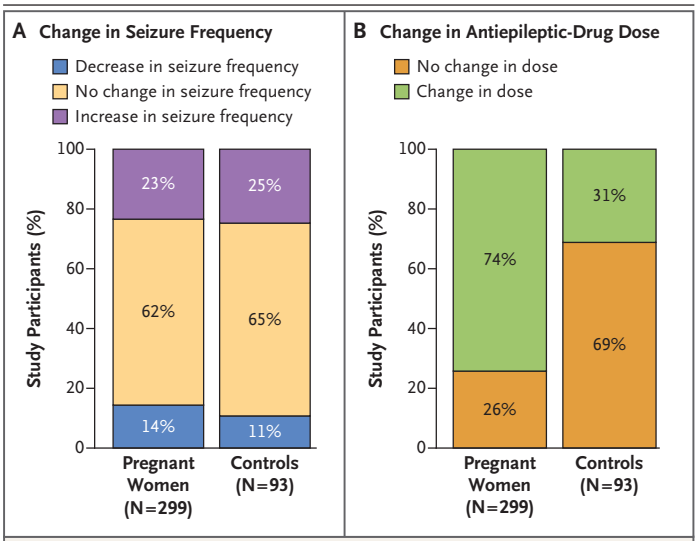

Figure 3. Changes in Seizure Frequency and Antiepileptic-Drug Dose.

Panel A shows the changes in the frequency of seizures that impaired awareness during epoch 1 as compared with epoch 2 in pregnant women and in controls (odds ratio for an increase in seizure frequency during pregnancy, 0.93; 95% confidence interval [CI], 0.54 to 1.60). Panel B shows the changes in the dose of an antiepileptic drug by the time of delivery in pregnant women and by 9 months after enrollment in controls (odds ratio for a change in dose during pregnancy, 6.36; 95% CI, 3.82 to 10.59).

adjusted for seizure type, antiepileptic drug category and group, presence of catamenial epilepsy, mother's IQ, and age (Table S8). No differences in the risk of an increased frequency of seizures were identified among different seizure types or drug categories or between groups in unadjusted or adjusted models. Results of post hoc sensitivity analyses were consistent with the findings of the primary analysis (Tables S9 through S12). Estimates of odds ratios from a post hoc analysis that was performed with imputation of missing data in the adjusted logistic-regression model for identification of risk factors were in the same direction as the estimates in the main analysis (Table S13).

DISCUSSION

During the past 20 years, prescribing patterns regarding antiepileptic drugs among pregnant women have changed at the same time that there has been a decline in the incidence of major congenital malformations[17] and in the frequency of adverse neurodevelopmental outcomes.[18-20] It is not known whether the use of antiepileptic drugs that have been associated with a relatively low risk of malformations has been at the expense of seizure control, as was initially reported with respect to lamotrigine and oxcarbazepine.[7,21,22] The EURAP, an international registry of antiepileptic drugs, reported no significant change over time in the percentage of women who had convulsive seizures during pregnancy, despite the increased use of antiepileptic drugs that have been associated with a decreased incidence of congenital malformations. This lack of change was attributed to a probable increased awareness of the need for monitoring of serum drug levels and dose adjustments during pregnancy.[17] However, pregnancy registries lack details about doses throughout pregnancy and a control group of nonpregnant women to inform such treatment decisions.

The main finding in our analysis was that there was no meaningful difference between pregnant women and nonpregnant women in increased seizure frequency during epoch 1 as compared with epoch 2. However, at the same time, the frequency of increases in drug doses was higher among pregnant women than among nonpregnant women. The frequency of seizures decreased in 14% of pregnant women and in 11% of controls between these two time periods.

Previous studies have suggested that seizures may increase during certain trimesters of pregnancy or during the peripartum period,[6,12,22] but we did not find differences between the pregnant women and controls according to pregnancy stage or seizure type, including convulsive seizures. The results for secondary outcomes showed that women who had no seizures during the 9 months before pregnancy or enrollment were more likely to remain seizure-free during pregnancy than those who had such seizures, findings that were similar to the results of previous studies.[10,23]

There are limitations of this study related to missing data and underpowering to detect between-group differences for specific seizure types. Although visit schedules to obtain outcome data were similar in the two groups, because of the observational study design, most pregnant women were monitored with routine measurement of antiepileptic-drug levels and dose adjustments to maintain the target-drug level they had before conception, a method that is consistent with national and international

recommendations.[24,25] The percentage of women who had at least one change in an antiepileptic-drug dose or an overall dose increase during pregnancy and a decrease in drug dose during the postpartum period was higher among pregnant women than among controls, a finding that was consistent with changes in drug clearance during pregnancy.[6,9,24,26-28]

Among women with epilepsy, the percentage who had a higher incidence of seizures that impaired awareness during pregnancy than during the postpartum period was similar to that in women who were not pregnant during the corresponding epochs. Changes in doses of antiepileptic drugs occurred more frequently in pregnant women than in nonpregnant women during similar time periods.

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