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Pregnancy Effects on Seizure Frequency: To Seize or Not to Seize

Changes in Seizure Frequency and Antiepileptic Therapy During Pregnancy

Pennell PB, French JA, May RC, et al. *N Engl J Med*. 2020;383:2547-56. https://pubmed.ncbi.nlm.nih.gov/33369356/. doi:10.1056/NEJMoa2008663.

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 2 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 2 epochs, seizure frequency was higher during epoch 1 than during epoch 2 in 70 (23%) pregnant women and in 23 (25%) controls (odds ratio, 0.93; 95% CI, 0.54-1.60). 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, 3.82-10.59). 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.)

Commentary

Educating women with epilepsy (WWE) about pregnancy is an important task given that approximately 1.5 million WWE are of childbearing age in the United States and give birth to 3 to 5 babies per 1000 born.[1] French et al[2] demonstrated that WWE, when compared with women without epilepsy, have comparable likelihood of achieving pregnancy, comparable time to achieve pregnancy, and comparable pregnancy outcomes (live births vs miscarriages). Despite this, some WWE may not consider having children because of their epilepsy. This may be related to many factors, but worry about increased seizure frequency and effects of anti-seizure medications (ASMs) are just a few that come to the forefront of clinical discussions. Anti-seizure medication management during pregnancy adds to the complexity of pregnancy management in WWE, with changes in clearance of some ASMs being one of the biggest concerns, along with risks of congenital fetal malformation development. Significant advances have been made in defining and differentiating risks reported among various ASMs. This has improved maternal and child outcomes and contributed to the fact that the majority of WWE have routine pregnancies and healthy babies. However, there are still many unanswered questions including how pregnancy truly effects seizure frequency and how to best manage ASM throughout pregnancy, all of which continue to emphasize our need as a community to increase our knowledge and education for these patients.

In the practice parameter update on the management issues for WWE in 2009,[3] it mentions that no study to date had compared change in seizure frequency in pregnant WWE to nonpregnant WWE. Thus, the recommendations stated there was insufficient evidence to support or refute a change in seizure frequency in pregnancy for WWE. This creates increased worry for WWE planning pregnancy and thus was an important void that needed to be addressed.

The article reviewed in this commentary took on the task to address the relationship between pregnancy and change in seizure frequency and to determine whether WWE experience a higher frequency of seizures during pregnancy then when they are not pregnant compared to a control group of nonpregnant WWE over a comparable time period. This is one of the first studies to use an appropriate nonpregnant comparator group of WWE. The study set forth to determine whether the percentage of WWE who had a higher frequency of seizures during pregnancy when compared with their postpartum period was greater than the percentage of seizure frequency change for nonpregnant women during the same period. The changes in doses of ASMs in these 2 groups were also assessed to help determine risk factors for increased seizure frequency during pregnancy. The study compared epoch 1 with epoch 2. Epoch 1 included pregnancy (enrollment date prior to 20 weeks gestation through delivery) and the peripartum period defined as the 6 weeks after birth. The control group was evaluated for 10.5 months post enrollment. Epoch 2 was the period from 6 weeks to 9 months after birth, or 7.5 months after the10.5-month period for the nonpregnant group. The participants used an electronic diary smartphone application to submit their information regarding seizure type and frequency as well as their ASM doses. The primary outcome measured the percentage of WWE who had a higher frequency of impaired awareness seizures during epoch 1 compared to epoch 2. Secondary outcomes evaluated the percentage of women who had increased frequency of seizures in each trimester and during the peripartum period, increase in other seizure types, percentage with change in dose of ASM, among others. Risk factors for an increased seizure frequency during epoch 1 compared to 2 in pregnant women were also assessed. A total of 352 pregnant women and 109 controls enrolled in the study. The results found that a frequency of seizures that impaired awareness was higher in epoch 1 than epoch 2 in 70 (23%) of 299 pregnant women and in 23 (25%) of 93 controls. In addition, the increase in seizure frequency in epoch 1 compared to epoch 2 was similar among the 2 groups within the trimesters and according to seizure type. Among the women who were seizure-free or convulsion-free during the 9 months prior to conception or enrollment, there were no between-group differences in epoch 1. At least one change in dose of ASM was reported in 222 (74%) of 299 pregnant women and in 29 (31%) of 93 controls by delivery or 9 months after enrollment. In 209 (70%) of the 299 pregnant women, the dose of ASM was higher by the end of pregnancy as compared to 22 (24%) of 93 in the control group.

In summary, these findings show that there was no meaningful difference among pregnant WWE and nonpregnant WWE in increased seizure frequency during epoch 1 as compared to epoch 2; however, there were higher increases in drug doses among the pregnant WWE group. Previous literature suggests that seizures may increase or worsen in severity in association with certain trimesters of pregnancy or during the peripartum period but this was not found in this study.[4,5] Rather there were no differences between pregnant women and controls according to the pregnancy stage or seizure type including generalized tonic–clonic seizures. In addition, the fact that there were more changes in anti-seizure drug dosing in the pregnant group confirms that changes in drug clearance are seen during pregnancy.[6,7] This also supports the need for ASM monitoring throughout pregnancy to maintain prepregnancy levels. This appears to reduce the risk of increased or worsened severity of seizures during pregnancy.

This publication provides more information about the causes of increased seizure frequency historically reported during pregnancy, illustrating that an increase in seizures may be more related to decreased levels of ASMs.[8] This is likely due to increased clearance associated with pregnancy as suggested by the observation that when pregnant WWE increased their doses of ASMs they were able to maintain a stable seizure frequency throughout their pregnancy. This further supports the need for compliance with increased drug level monitoring during pregnancy. Continued information in this area of study allows clinicians to refine treatment choices and dosing strategies more effectively throughout pregnancy in WWE. Specific published guidelines on which ASMs to test and when to test throughout the pregnancy would be helpful. Educational material for WWE should address that seizure frequency during pregnancy is similar to the nonpregnant period with careful ASM monitoring and thus reassure WWE and their care providers. This publication should decrease the anxiety around pregnancy for WWE for both the patient and the provider as well as improve their care.

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