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Cutting the Losses of Pregnant Women With Epilepsy

Association of Unintended Pregnancy With Spontaneous Fetal Loss in Women With Epilepsy: Findings of the Epilepsy Birth Control RegistryHerzog AG, Mandle HB, MacEachern DB. *JAMA Neurol*. 2018. doi:10.1001/jamaneurol.2018.3089. [Epub ahead of print] PMID: 30326007.

Importance: If unintended pregnancy is common among women with epilepsy and is associated with increased risk of spontaneous fetal loss (SFL), it is important to develop guidelines for safe and effective contraception for this community. Objective: To assess whether planned pregnancy is a determinant of SFL in women with epilepsy. Design, setting, and participants: The Epilepsy Birth Control Registry conducted this web-based, retrospective survey between 2010 and 2014. It gathered demographic, epilepsy, antiepileptic drug (AED), contraceptive, and reproductive data from 1144 women with epilepsy in the community between ages 18 and 47 years. Data were analyzed between March 2018 and May 2018. Main outcomes and measures: The primary outcome was the risk ratio (RR) with 95% confidence intervals (CIs) for SFL in unplanned versus planned pregnancies. The secondary outcome was the identification of some potentially modifiable variables (maternal age, pregnancy spacing, and AED category) of SFL versus live birth using binary logistic regression. Results: The participants were proportionally younger (mean [standard deviation] age, 28.5 [6.8] years), and 39.8% had household incomes of $25 000 or less. Minority women represented only 8.7% of the participants. There were 530 (66.8%) of 794 unplanned pregnancies and 264 (33.2%) of 794 planned pregnancies. The risk of SFL in 653 unaborted pregnancies in women with epilepsy was greater for unplanned (n = 137 of 391; 35.0%) than planned (n = 43 of 262; 16.4%) pregnancies (RR: 2.14; 95% CI: 1.59-2.90; $P < .001$). Regression analysis found that the risk of SFL was greater when planning was entered alone (odds ratio [OR], 2.75; 95% CI: 1.87-4.05; $P < .001$) and more so when adjusted for maternal age, interpregnancy interval, and AED category (OR: 3.57; 95% CI: 1.54-8.78; $P = .003$). Interpregnancy interval (OR: 2.878; 95% CI: 1.8094-4.5801; $P = .008$) and maternal age (OR: 0.957; 95% CI: 0.928-0.986 for each year from 18 to 47 years; $P = .02$), but not AED category, were also associated. The risk was greater when interpregnancy interval was less than 1 year (n = 56 of 122; 45.9%) versus greater than 1 year (n = 56 of 246; 22.8%; RR: 2.02; 95% CI: 1.49-2.72; $P < .001$). Relative to the younger than 18 years cohort (n = 15 of 29; 51.7%), the risks were lower for the intermediate older cohort aged 18 to 27 years (n = 118 of 400; 29.5%; RR: 0.57; 95% CI: 0.39-0.84; $P < .004$) and the cohort aged 28 to 37 years (n = 44 of 212; 20.8%; RR: 0.40; 95% CI: 0.26-0.62; $P < .001$) but not significantly different for the small number of participants in the aged 38 to 47 years cohort (n = 3 of 12; 25.0%). No individual AED category's SFL frequency differed significantly from the no AED category. Conclusions and relevance: The Epilepsy Birth Control Registry retrospective survey finding that unplanned pregnancy in women with epilepsy may double the risk of SFL warrants prospective investigation with outcome verification.

Commentary

In utero exposure to antiepileptic drugs (AEDs) increases the risk of negative outcomes in children of women with epilepsy (WWE). These children are at higher risk of major congenital malformations, neurodevelopmental delay, low birth weight, and size small for gestational age. Pregnancy planning is essential in order to minimize these risks. However, there are many factors that often prevent successful pregnancy planning including limited access to epilepsy care, education, and counseling, as well as inappropriate contraceptive methods.

Unintended pregnancy is common among WWE. The retrospective data from the Epilepsy Birth Control Registry (EBCR) web-based survey of 1144 WWE, in the community between 18 and 47 years of age, revealed that most of them (78.9%) had at least one unintended pregnancy and that 65% of their pregnancies were unintended.[1] An analysis of women across 13 states who participated in The Pregnancy Risk Assessment Monitoring System, an annual survey of randomly sampled postpartum women administered by the Centers for Disease Control and Prevention, revealed that 55% of pregnancies were unintended in WWE.[2] In both surveys,

younger maternal age was found to contribute to the higher rates of unintended pregnancies in WWE compared to women without epilepsy.

While many WWE do not have access to subspecialized care by an epileptologist, even the ones who have access to it may not receive appropriate education and counseling about pregnancy planning and contraceptive methods. In a retrospective chart review of female patients aged 18 to 45 seen at a major academic center for an initial visit, only 35% of them were counseled about contraception at the first visit.[3] The investigators also found that if women were not counseled at the first visit, they were unlikely to be counseled at subsequent visits; only 37% had ever received counseling by their fourth visit.[3] In addition, epileptologists often leave to gynecologists and patients the task of selecting the contraceptive method. Many patients are unaware of important drug–drug interactions between AEDs and hormonal contraception that can lead to contraceptive failure.[4] Discussing appropriate contraception is an important part of managing WWE and should be addressed by both the epileptologist and the gynecologist. Both the Centers for Disease Control and Prevention and the World Health Organization have released evidence-based reviews and opinions on the use of contraception in WWE.[5,6] The most reliable form of reversible contraception for any woman is the intrauterine device (IUD), and this is considered the method of choice for most WWE. When the use of an IUD is not possible, combined hormonal birth control methods, including the pill, the patch, and the vaginal ring, are acceptable options for most women on nonenzyme inducing AEDs. Unfortunately, fear of worsening seizure frequency with the use of exogenous hormones prevents some women from using hormonal contraception, but the data on this subject are scarce. While the interim findings of the EBCR suggested that the rates of seizure increase associated with hormonal contraception (21%) are greater than with nonhormonal contraception (3.9%), the differences may reflect biological effects or reporting bias, and further investigation is needed before we can use these data to advise patients against the use of hormonal contraception.[7] In addition, WWE often encounter socioeconomic and psychosocial barriers that women in the general population do not experience. These barriers may influence their behavior and interfere with their decision-making, resulting in unintended pregnancies.

It has been established that in the general population, a high proportion of unplanned pregnancies end in abortion, and unintended pregnancies may be at increased risk of poor birth outcomes including spontaneous fetal loss (SFL).[8] Given the risks posed by AEDs and seizures, one may expect that this will also be the case in unintended pregnancies of WWE. The most recent investigation from the EBCR—the subject of this commentary—found that unplanned pregnancy in WWE may double the risk of SFL, suggesting once more that pregnancy planning is of utmost important for WWE. A short inter pregnancy interval and young maternal age, but no AED category, were also associated with an increased risk of SFL in WWE. A prospective study from the European and International Registry of Antiepileptic Drugs in Pregnancy concluded that the most important risk factors for intrauterine death in pregnancies of WWE include maternal exposure to AED polytherapy and the presence of major congenital malformations in at least one of the parents.[9] Rates of intrauterine death were similar across the different monotherapies, but higher with polytherapy.

It is unclear if the risk of SFL is higher in WWE when compared to the general population. A prospective study evaluating the incidence of SFL among WWE and the wives of men with epilepsy revealed that the cumulative risk of spontaneous abortion of 18% for AED-exposed pregnancies was similar to risks reported in the nonepilepsy population.[10] Thus, neither epilepsy nor in utero AED exposure was found to be associated with recognized fetal loss. However, other publications suggest the contrary. A publication from the Kerala Registry of Epilepsy and Pregnancy found that WWE have an increased risk of spontaneous abortions.[11] But even if the incidence does not differ, understanding the specific risks of SFL in WWE is essential.

The findings from the EBCR are valuable but limited by its self-reported nature and the possibility of selection bias. In addition, this web-based survey captures a specific portion of the WWE population that includes younger and better educated women with an underrepresentation of minorities. Prospective observational studies looking into this subject are needed in order to confirm these findings.

By Naymee Velez-Ruiz

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