Pregnancy and Epilepsy: A Guide to Treatment and Management of Risks

Research is offering new paths in the management of women who are or may become pregnant.

With Cynthia Harden, MD

Managing a chronic medical condition for a patient who is pregnant can be a high-wire balancing act that can test a physician’s prowess. The decision to treat a patient (as well as selecting an optimal regimen) is the result of careful consideration of several continually shifting factors. This is particularly evident in the realm of epilepsy, in which the condition itself poses health risks for both the pregnancy and the patient. Therefore, physicians often tread carefully when it comes to treatment, to ensure that the patient is receiving appropriate care while minimizing risks.

In addition to broad concerns regarding pregnancy and epilepsy treatment, the relationship of epilepsy and fertility has received attention of late. In particular, studies have increasingly indicated that patients with epilepsy have lower birth rates than the general population.

Despite many unanswered questions and a variety of challenges in the management of women with epilepsy who are or may become pregnant, Cynthia Harden, MD, Professor of Neurology at Mount Sinai Hospital in New York, believes that the evolving research spectrum is elucidating the complex relationship of epilepsy and pregnancy, which may increasingly yield viable approaches to care. Ahead, Dr. Harden shares insights on the latest research and developments on the topic.

Quality Measures and Discussion of Risks

For women of childbearing age as well as those who are pregnant, selecting the right anti-epileptic drugs (AEDs), i.e. those that are compatible with hormonal birth control, can be as significant a challenge as selecting an agent that’s associated with low risk during pregnancy, according to Dr. Harden. “It turns out that there is not enough information about many of the AEDs that do not have hormonal interactions,” says Dr. Harden, who notes further that well-informed choices are still limited. “We may make decisions based on what we don’t know rather than what we do know.”

One of the challenges of treating any woman of childbearing age is how much emphasis to place on her intentions regarding pregnancy. “When you have a new patient in front of you, she might be thinking of contraception, but there is always a chance that she changes her mind or becomes accidentally pregnant,” says Dr. Harden. Therefore, “discussion of teratogenesis and risk when taking medicines is always present.”

In 2009, the American Academy of Neurology incorporated language into its quality care measures regarding the importance of, at least once per year, having a conversation about risks with women with epilepsy of childbearing age. The inclusion of this measure cannot be understated, according to Dr. Harden. “The Academy’s quality measures help us to provide thoughtful, uniform care, and this is one

PRACTICAL POINTERS

Despite many unanswered questions and a variety of challenges in the management of women with epilepsy who are or may become pregnant, the evolving research spectrum is improving our understanding of the complex relationship of epilepsy and pregnancy. Additionally, the role of epilepsy in fecundity may be less important than previously thought, as new research has found that pregnancy rates among women with epilepsy who are actively trying to conceive are no different than those of women who do not have epilepsy.
of the few evidence-based quality measures we have to manage risks.” The measure has survived the recent revision to the quality measures, which, according to Dr. Harden, is a positive reflection of the important role such conversations play in modern epilepsy care.

**Treatment Selection Nuances**

When selecting medications for patients with epilepsy who are pregnant or may become pregnant, there is a set of medications that are safer to use during pregnancy, Dr. Harden points out. Moreover, an expanding data set is helping to inform those choices. “Overall, based on worldwide pregnancy registries, the choices of safer AEDs for pregnancy include levetiracetam, carbamazepine, oxcarbazepine, zonisamide, lamotrigine, and phenytoin.”

Where treatment becomes challenging, however, is in the specifics of managing individual cases. Choosing a medication for a patient with a new diagnosis who may become pregnant, for example, requires the physician to consider a variety of present and potential factors. But according to Dr. Harden, one tenet that applies in most situations is to ask patients to take folic acid at least 1mg per day. “This prevents birth defects in general and, specifically for the epilepsy population, it’s associated with mitigating adverse events of cognitive outcomes associated with drug exposure.” The drug exposure component is crucial, she says. “If you are not taking medicines, the risks are pretty much the same as for the general population, as the literature seems to indicate that there is not much risk in having epilepsy itself.”

But when it comes to individualizing treatment based on certain patient or drug conditions, selection becomes very difficult. For example, in the case of someone is already pregnant and currently on a medicine that has a high risk of causing birth defects and adverse cognitive outcomes, there is no accepted guideline on whether to continue the drug, change altogether, or adjust the dose, says Dr. Harden. “The two reasons we might change anti-seizure medicine are continuing seizures or side effects,” she offers. For continuing seizures, the decision to change medications or alter the regimen is a bit easier. “We try to find a medicine that’s appropriate for the patient’s seizure type and we add it in, thinking about drug interactions and setting parameters for what you will call success or failure,” Dr. Harden observed.

Importantly, the epilepsy community has adopted a new definition of refractory epilepsy, Dr. Harden imparts. “If you fail two AEDS used at good doses you are considered medically refractory. That should prompt referral to epilepsy center to consider whether surgery should be considered.” The basic idea is that if a patient is not going to respond to medication, that often declares itself fairly early, Dr. Harden observes. “One really interesting phenomenon about epilepsy is that for patients who are medication resistant, it’s very hard to find that magic bullet after two medications.” Therefore, she observes that medication-resistant patients are almost a separate population entirely from other patients. “About 70 percent of patients are relatively easy to control, and those that fall into the lesser percentage of medication-resistant patients are often the most difficult to manage.”

When considering a switch in patients who are already pregnant, it is best to avoid switching to a medicine that the patient hasn’t already tried, according to Dr. Harden. “Ideally, you want to find anything the patient took in the past that’s well tolerated,” says Dr. Harden. If you are adding a medicine to an existing regimen, the most beneficial choice is the most broad-spectrum agent with the least potential for side effects, especially allergy,” says Dr. Harden. Levetiracetam tends to be favored in this regard, since it does not have any significant interactions and has a low risk of allergy.

Also worth noting in the context of changing a regimen is the increasing evidence regarding dose, says Dr. Harden. Monitoring anti-seizure drug levels prior to pregnancy can help gauge a sense of each patient’s individualized therapeutic level, Dr. Harden suggests. “You really want the patient to maintain seizure freedom during pregnancy, and she’s very likely to do so if that level is maintained. You want to achieve the lowest level of exposure that is associated with seizure freedom prior to pregnancy, and then during the pregnancy it’s about maintaining that level, keeping in mind that some of the medical levels do drop quite a bit,” she observes.

Take, for example, lamotrigine, which Dr. Harden notes is one of the most widely used medicines due to its effectiveness, tolerability profile, and low teratogenicity. “Roughly 70 percent of women who take lamotrigine are subject to hormonal interactions, and when they become pregnant the clearance goes up by about 200 percent.” She notes further that seizure exacerbation has been associated with both lamotrigine and oxcarbazepine, underlining the importance of devising a strategy for managing these patients. Levetiracetam may also be associated with a decrease in these levels during pregnancy, but Dr. Harden notes that it may not have as close an association with seizure occurrence, “possibly due to the differential effect of the drug in the brain versus blood levels.”

One study found that patients seem to have a more pronounced risk of seizures when levels dropped to 35 percent below the target therapeutic level.1 “It appears that once you get to a 35 percent drop from the level that was defined before pregnancy you may be getting into riskier territory,” says Dr. Harden.
Fecundity and Epilepsy

As the neurology community has increasingly recognized and addressed the challenges of treating patients with epilepsy who are or may become pregnant, questions related to fertility and epilepsy have persisted without as much research attention. “There is a body of literature showing that birth rates are lower among people with epilepsy—men and women,” says Dr. Harden. The question of why those with epilepsy are less likely to have children has not been sufficiently addressed, according to Dr. Harden. This was the basis for a study that Dr. Harden and co-investigators Page B. Pennell, MD and Jaqueline A. French, MD presented at the American Academy of Neurology Annual Conference earlier this year, entitled “A Prospective Study of Pregnancy in Women with Epilepsy Seeking Conception (The WEPOD Study).”

“I have always been trying to understand whether these lower birth rates are a result of infertility, a conscious choice patients make, or just that a fraction of people with epilepsy are disabled and not going to have children,” says Dr. Harden. “We did the first prospective study of patients with epilepsy who were trying to get pregnant and compared them to a set of healthy controls. In a sense, we were trying to prove or disprove this idea that women with epilepsy have greater rates of infertility or lesser rates of fertility,” she observes. The study tracked menstruation, medicine, seizures, and frequency of sex through the use of an app. “Patients had to have been trying for pregnancy and off of birth control for no less than six months and we followed them for 12 months prospectively, with fecundity rates being our primary outcomes,” says Dr. Harden. The study included women who were deemed overall healthy but excluded women with polycystic ovarian syndrome. “We weren’t overly exclusive because we wanted to be able to project this information to a general population,” notes Dr. Harden.

The overall pregnancy occurrence was 70 percent in the epilepsy group and 67 percent in the healthy controls, accounting for dropouts, which were about 14 percent in the epilepsy group and 20 percent in the healthy controls. “If you look at the rates over time, the outcomes were nearly the same,” says Dr. Harden. This holds true across live births as well as miscarriages, which, according to Dr. Harden, were 13 percent in the epilepsy group and 20 percent in the healthy controls.

The results indicate that fertility rates of those with epilepsy may not be different at all, a potentially significant finding. However, Dr. Harden notes that much remains to be learned about this phenomenon. A similarly designed study conducted in India yielded comparable results, however it also included treatment implications.2 “One key finding to emerge in that study is a potential adverse effect of more powerful enzyme inducing AEDs differentially on getting pregnant,” observes Dr. Harden. The effect of anti-seizure medications on the ability to become pregnant represents the next step for Dr. Harden and her team.

In terms of broader next steps, Dr. Harden notes that the fecundity study she recently carried out with her co-investigators has already revealed provocative neuroendocrine influences on epilepsy. From additional hormonal analyses carried out on the study subject, it was discovered that anti-mullerian hormone (AMH) may affect seizure occurrence. “Anti-mullerian hormone is a peptide hormone that associates with brain volume in women with multiple sclerosis, and is highly neuroprotective in stroke models as well. Our findings suggest that it may play a role in epilepsy and serve as a link between reproductive function and epilepsy,” says Dr. Harden.

Another positive aspect of the study is the WEPOD app itself, which has already been adopted for use in other studies. With the app, tracking and documenting seizure activity is much easier and possibly more reliable, which is beneficial for both the participant and the researcher. “The creativity around this study is likely going to have lasting effects in research efforts going forward,” she says. “Hopefully we have contributed to science and the field.”

Conclusion

As new research continues to shed light on the relationship of epilepsy and pregnancy, Dr. Harden notes that pregnancy registries can help bolster these efforts. “Women with epilepsy who are pregnant should participate in the pregnancy registry, so that, especially with the newer anti-seizure medications, information regarding their use can be used to help all families with members who have epilepsy.” Patients can register online at www.aedpregnancyregistry.org. Yet despite the increased awareness and both in research and in practice, Dr. Harden implores that many questions have yet to be answered, particularly with regards to the risks of treatment during pregnancy. “Although national and international pregnancy registries have immensely increased our ability to safely navigate pregnancy for a mother with epilepsy, the risks in pregnancy associated with anti-seizure medications during pregnancy is still not fully known,” she says. “In the future, we will likely achieve a much greater understanding of the effect of levels and of medication combinations on pregnancy risks.”

Cynthia L. Harden, MD is a Professor of Neurology at Mount Sinai Hospital in New York.