PRACTICE CURRENT: An interactive exchange on controversial topics
Luca Bartolini, MD, *Section Editor*

How do you treat epilepsy in pregnancy?

Ilena C. George, MD

Epilepsy affects millions worldwide and women of childbearing age constitute between 25% and 40% of all patients with epilepsy.^{1,2} Estimates based on the population in the United States in the 1990s approximate that 25,000 children are born to women with epilepsy (WWE) annually.^{3,4} For WWE who are pregnant or planning to become pregnant, providers should consider the potential risks regarding seizure control, obstetric complications, and teratogenicity of antiepileptic drugs (AEDs) when counseling patients and determining a treatment plan.^{5,6} Studying pregnant women poses unique challenges. Randomized control trials are difficult to conduct in this population, and much of the available data is observational by necessity, which precludes many studies from reaching the most rigorous levels of evidence. Several aspects of the care of pregnant WWE are discussed in this commentary, with a special focus on teratogenicity and drug monitoring.

Contraception and prepregnancy planning

The first trimester is the most vulnerable period for fetal development; however, a high rate of pregnancies in WWE—estimated at 65%—are unplanned and may not be recognized until after this time.⁷ One of the possible causes of this high unplanned pregnancy rate is the interaction between hormonal contraception and enzyme-inducing AEDs, leading to decreased efficacy in preventing pregnancy.

As part of prepregnancy planning, folic acid supplementation is often recommended. Evidence for the role of folic acid in preventing major congenital malformations (MCMs) is mixed. Ban et al⁸ found no difference between MCM rates between WWE on high-dose folic acid (5 mg) and those on low or no folic acid (adjusted odds ratio [aOR] 1.75, 95% confidence interval [CI] 1.01–3.03 vs aOR 1.94, 95% CI 1.21–3.13), although a significant confounder was that a large number of participants were not taking this

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supplementation in the earliest months of pregnancy. A prospective study from the UK Epilepsy and Pregnancy Register also found no reduction in MCM risk in the folic acid group.⁹ However, there is also evidence for higher mean IQ in children whose mothers took at least 0.4 mg folate periconceptionally (IQ 108, 95% CI 106–111, $p = 0.009$ compared to control).¹⁰ The American Academy of Neurology's Practice Parameters recommended folic acid supplementation of at least 0.4 mg daily in all women of childbearing age as it is generally a benign intervention and may prevent MCMs.⁵

There have been demonstrated benefits to planned pregnancy in WWE. Ideally, prior to pregnancy, WWE and their physicians should optimize their AED regimen by using the lowest effective dose, especially if treatment with AEDs with higher teratogenic risk is necessary.¹¹ A small retrospective study of 153 WWE found that those who are able to plan their pregnancies were more likely to be on monotherapy (80% vs 61%, $p = 0.049$), to avoid valproic acid (VPA) in the first trimester (77% vs 56%, $p = 0.031$), and to have a lower frequency of convulsive seizures (16% vs 35%, $p = 0.018$).¹²

Seizure frequency during pregnancy

Seizures during pregnancy may pose risks of obstetric complications and risks to the developing fetus, although there is no clear consensus in the literature consistently identifying these risks. Seizure activity during pregnancy may increase risk of preterm birth, low birthweight, and small for gestational age births.² Regardless of whether seizures occur during pregnancy, WWE may have increased likelihood of certain complications in fetal development, particularly restricted uterine growth.^{13,14}

In general, most WWE will remain seizure-free during pregnancy; epilepsy pregnancy registry data estimate seizure freedom in 50%–67% of WWE.^{15–17} Prepregnancy seizure control predicts seizure control during pregnancy. The Kerala Registry of Epilepsy and Pregnancy study reported that seizure control in the month prior to pregnancy was the greatest predictor of seizure freedom during pregnancy, with an odds ratio (OR) of 13.6 (95% CI 7.6–24.4) for seizures during pregnancy if seizures had occurred in the month prior to pregnancy. Another group showed risk of seizure during pregnancy was 24.9% when seizure freedom had been maintained for 1 year prior to pregnancy.¹⁶ Use of multiple AEDs, suggesting more difficult to control epilepsy, was also a significant predictor of seizure activity during pregnancy (OR 3.0, 95% CI 2.3–3.9).¹⁷

Antiepileptic drugs and risk of congenital malformations

Given the limited feasibility of randomized control trials in pregnant women with regards to AEDs and the large numbers of participants needed to demonstrate causality, epilepsy pregnancy registries have provided data on congenital malformation rates and relative safety of AEDs. Overall, rates of major congenital malformations (MCMs) are estimated at 4%–9% among WWE on AEDs compared to 1%–2% in the general population.^{18,19} Rates are higher in patients on polytherapy.²⁰

Of the AEDs available today, VPA has been linked to a variety of MCMs at the highest rate, between 6% and 14%.¹ Initially linked to spina bifida, other malformations caused by early exposure to VPA include cleft palate, cardiac abnormalities, and hypospadias, among others.²¹ A dose-dependent relationship between VPA and MCMs has been demonstrated.¹¹ Doses higher than 700 mg per day, and especially higher than 1,500 mg per day, have shown significantly increased rates of MCM.^{1,22} There has also been evidence for cognitive impairment or learning delay in multiple domains in children exposed to VPA in utero, a significant decrease in IQ scores, and a possible increased risk of autism spectrum disorders.^{23,24} Data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study found a dose-dependent effect of VPA on lowering IQ (mean 97, 95% CI 94–101) compared to children exposed to carbamazepine ($p = 0.0015$), lamotrigine ($p = 0.003$), and phenytoin ($p = 0.0006$).¹⁰

For some patients, valproate is key to seizure control. EURAP data demonstrated that in patients on VPA seizure freedom was obtained more frequently than those on the other AEDs studied (75%); lamictal was the least likely to provide seizure freedom (58.2%, $p < 0.0001$).¹⁵ A smaller subset of data from EURAP comparing patients who stopped VPA in the first trimester to those who remained on this medication or switched to a different AED found that generalized tonic-clonic seizures were twice as common in the withdrawal or switch groups.²³

Phenytoin, phenobarbital, and carbamazepine have shown significantly increased rates of MCM compared with WWE on lamotrigine and pregnant women without epilepsy.²⁵ A recent Cochran Database article reported no significant difference in the rates of MCMs among these 3 medications; the pooled prevalences were 4.93% (carbamazepine), 7.10% (phenobarbital), and 6.26% (phenytoin).²⁶ Phenobarbital was significantly more likely to cause cardiac malformations than phenytoin or carbamazepine.²⁶ Although the EURAP group found evidence for dose-dependence and increased risk of MCM across AEDs,¹⁵ other registry studies have not consistently demonstrated this relationship.^{1,18,25} Topiramate has been associated with increased risk of cleft abnormalities, as well as low birth weights and small for gestational age infants.^{1,25,27}

Emerging data on newer AEDs as monotherapy have demonstrated the relative safety of levetiracetam,^{19,28} lamotrigine,¹⁹ oxcarbazepine, and zonisamide²⁹ in WWE who are pregnant; however, data are more limited for the latter two. Levetiracetam and lamotrigine in particular have not been associated with increased risk of MCM compared to controls and are generally considered safe to use in pregnancy.^{1,19}

Monitoring drug levels

Clearance of AED changes in pregnancy, which has implications for how often providers should monitor serum levels of certain agents. Lamotrigine levels in particular can drop precipitously at any point in pregnancy, but most notably in the third trimester, and is likely related to enzymatic induction and the cytochrome p450 system.²⁶ This should prompt providers to increase the dosing of this medication. The EURAP trial demonstrated that of the AEDs studied, patients on lamotrigine most commonly required adjustments to their medications, likely from levels falling in pregnancy.¹⁵ There is a paucity of data on levels of newer AEDs in pregnancy and changes in levels vary across individuals, however, the metabolism rate of levetiracetam in particular seems to increase in pregnancy.²⁶

Expert opinions

Three experts were asked to comment on the following cases:

1. What medication would you start in a 21-year-old woman with focal epilepsy of unknown etiology, not on anti-epileptics, who presents for a first-time clinic appointment? How do you counsel her when she returns for follow up and is considering pregnancy?
2. What medication changes, if any, do you recommend in a 24-year-old woman with juvenile myoclonic epilepsy controlled with valproic acid 750 mg and lamictal 200 mg twice a day?

Dr. Cynthia Harden (USA)

Prepregnancy planning in patients with epilepsy of childbearing age is particularly important. I routinely recommend folic acid of 0.8 mg. I use this dose because the dose that is associated with good pregnancy outcomes is unknown, but in the NEAD Study Group, 0.4 mg significantly affected cognitive outcomes.¹⁰ Since we have folic acid supplementation in food in this country, without a family history of birth defects I would recommend this dosage. At a first visit I would have a discussion about birth control as well. I try to really pin people down on birth control strategies; it can be problematic to have an unplanned pregnancy when a patient is taking antiepileptics. In this patient, I would probably start levetiracetam first. If she is on birth control I would go with levetiracetam and if she is not on birth control I might go with lamotrigine. This way if the patient does

become pregnant, she is on a medication with the lowest teratogenic risk. When the patient comes back to discuss pregnancy, my concern would be seizure control, but teratogenicity is a close second. It seems to me from the literature that the risk of obstetric complications is related to antiepileptics, unless the patient has uncontrolled seizures. Breastfeeding when on antiepileptic drugs appears to be safe in pregnancy. For monitoring drug levels, I would check a level of the drug at least once while the patient is doing well, prior to pregnancy, and then at least every trimester. For lamotrigine, I would check soon after learning the patient was pregnant; if the patient has increased metabolism of lamotrigine, she is likely to have increased clearance early on. That way you will know you will need to follow the level every 2–4 weeks. After delivery, I try to get a level while the patient is still in the hospital as deinduction happens within a few days. Twenty-five percent of women on lamotrigine will not have a change in pregnancy. If the patient is taking carbamazepine, that tends to be very stable and I might check once every trimester. For patients on levetiracetam I would check about once a month. Zonisamide and topiramate levels also tend to fall and may require a dose increase. For most medications, one strategy is to also check a level near the end of the third trimester to make sure the level is in a good range prior to labor. In case 2, I might not change her medications but if I did I would decrease her valproate because the effect on cognitive outcomes can be related to exposure after the first trimester. There is a dose dependence to risk of malformations on valproate. I would look at what her levels are and try to learn more about her history of antiepileptic drug use. I would try to get a sense of whether she had seizures on previous doses of valproate, and if lamotrigine or valproate was the more important drug for seizure control for her.

Dr. Torbjörn Tomson (Sweden)

Developing a strong relationship with patients is as a fundamental part of treating their epilepsy. Pregnancy planning in patients with epilepsy, including a discussion about contraception, should start from a first visit. If the patient in case one is not planning a pregnancy, I do not prescribe extra folate. My first choice for antiepileptic medication would be carbamazepine for a focal epilepsy but if the patient is using hormonal contraceptives I would make another choice. When the patient returns stating she is planning a pregnancy, I would want to know 2 things: was it difficult to control her epilepsy and if she had focal seizures, did she have bilateral spread to a generalized tonic-clonic seizure? These would increase my concern about seizure control in pregnancy. Otherwise I would be concerned about teratogenicity. I do increase the frequency of checking levels in pregnant patients, in particular for lamotrigine, levetiracetam, and oxcarbazepine. How often I check depends on the prior history of the patient; if a patient is sensitive to small changes in dose I would check more frequently. In general I would check anywhere between monthly and bimonthly. I try to adjust medications before patients have breakthrough seizures; I do not wait for the seizure. If I have a female patient of childbearing age, I try to get a baseline blood level before she becomes pregnant or early in pregnancy. In case 2, if the patient is presenting after week 8 or so of pregnancy, changing her medications would not have an effect on the risk of malformations, but possibly on cognitive development, and I would like to know if there are any indications she is on a higher dose of valproate than necessary. In adjusting her medications, my main aim would be to try to reduce the dose of valproate. I would like to know more about how this patient came to be on high doses of her medications. For instance, was she carefully titrated up to this dose or was she on a higher dose of valproate and this was gradually decreased after adding lamotrigine?

Dr. Augustina Charway-Felli (Ghana)

It is important to counsel patients, especially at a first visit. The most common medications used in epilepsy in the population I treat are phenytoin, carbamazepine, valproate, and phenobarbital. Lamotrigine, levetiracetam, and topiramate are also available in Ghana

but often patients cannot afford them. Ghana's national health insurance scheme covers basic drugs such as phenytoin, carbamazepine, and valproate, but these are not always readily available in the pharmacies. Patients have to pay out of pocket for brand name drugs. Also, many patients are not covered by insurance. For case 1, I do not routinely recommend folic acid supplementation in patients with epilepsy but will start supplementation in patients who are pregnant or planning to become pregnant. Here, folic acid is available in 5 mg tablets. In someone coming in for a first-time visit, as in this case, I would avoid phenytoin and valproate and explain to the patient why. If valproate is the drug of choice, I would explain why it is risky and why I would want to try a different medication. For instance, I have had patients with juvenile myoclonic epilepsy and I have long discussions with the patients and often their parents about teratogenic risks and the need to prevent pregnancy while on treatment. If the patient was not female, I would give valproate, but in this case I would give levetiracetam if the patient can afford it. When the patient returns discussing planning a pregnancy, my first concern would be teratogenicity, then seizure control. I do not routinely monitor antiepileptic drug levels. I only check levels if there are breakthrough seizures or continuing seizures despite optimum levels of antiepileptic medications. In our setting, because of poverty, sometimes patients state they are compliant when they are not. That is often when I check levels; I would like to check more often but it is financially not viable. Compliance is a huge problem where there is poverty: sometimes patients will split their medications and the quality of drugs they can afford also has an effect. In case 2, I would try to decrease the valproate and increase folic acid. If she remains seizure-free I would see if I could change the lamotrigine as well, although to err on the side of caution I would leave her on lamotrigine. The patient would have to be counseled on the risk of malformations and cognitive impairment in the baby.

Preliminary survey results (June 20, 2017): Section Editor Luca Bartolini, MD

We collected a total of 269 complete questionnaires since May 31, 2017, half from epileptologists and half from general neurologists. Eighty-two responders (30%) stated they had seen 10 or more pregnant women with epilepsy over the last 12 months. Forty percent of survey takers have been in practice for less than 10 years, 40% for 10 or more years, and 20% were still in training. A total of 62% practice outside of the United States.

For the first case about a 21-year-old woman who is diagnosed with focal epilepsy of unknown etiology, while the overwhelming majority of responders ($n = 214$, 81%) recommended folic acid supplementation, results highlighted uncertainty about the dosage: 34% chose 4 mg, 17% chose 2 mg, 13% chose 0.8 mg, and the same percentage chose 0.4 mg (figure, A).

Unsurprisingly, the majority of survey takers recommended to start lamotrigine ($n = 120$, 45%) or levetiracetam ($n = 86$, 32%), a choice that seems supported by emerging data on safety of newer AEDs. Teratogenicity was the foremost concern regarding AED use in pregnancy ($n = 173$, 65%) and seizure control was second ($n = 90$, 34%). The majority of responders monitor AED levels in pregnancy ($n = 207$, 78%), at monthly intervals (44%) or once a trimester (27%), particularly for the following AEDs (chosen by 50% or more of survey takers who check levels): carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, and valproate.

Uncertainty prevailed in the second case about a 24-year-old woman with juvenile monogenic epilepsy controlled on valproate and lamotrigine who is in the first trimester of pregnancy. When confronted with a difficult decision whether to change the therapeutic strategy that worked but included valproate, half of respondents ($n = 142$) recommended to keep the status quo, and half ($n = 123$) chose to make a change (figure, B). Of those

Figure Interactive world map of preliminary results

(A) Snapshot of the interactive world map with pie charts representing dosage of choice for folic acid supplementation in a woman of childbearing age with focal epilepsy. Thirty-four percent of responders chose 4 mg (gray slice), 17% chose 2 mg (red slice), 13% chose 0.8 mg (blue slice), and the same percentage recommended 0.4 mg (teal slice). (B) Snapshot highlighting lack of consensus across the globe about decision to modify therapy in a pregnant woman with juvenile monogenic epilepsy controlled on valproate and lamotrigine: 53% recommended to keep medications unchanged (teal slice) and 46% chose to modify the therapy (blue slice). The size of all pie charts is proportional to the number of responses from each country or state.

who recommended a change, 56% chose to stop valproate and 38% to reduce valproate dosage. Lowering the dose may be a trade-off between the risk of major congenital malformations/cognitive impairment and seizure recurrence, but this remains an individualized decision, as highlighted in the expert opinions. Eighty percent of responders ($n = 213$) did not recommend to start a new medication, and those who did primarily chose levetiracetam.

CONCLUSION

Women with epilepsy who are of childbearing age present a unique challenge. Counseling and prepregnancy planning are essential in the approach to treatment of women with epilepsy as unintended pregnancies occur at a high rate in this population, implying a high rate of accidental exposure to AEDs during organogenesis. VPA has dose-dependent teratogenic effects and also affects cognitive development of children born to WWE. Newer AEDs such as levetiracetam and lamotrigine appear to have lower risks of MCMs compared with VPA, phenytoin, and phenobarbital. Seizure control prior to pregnancy predicts seizure control during pregnancy,

but to minimize teratogenic risk, WWE should be on the lowest effective dose of AEDs prior to pregnancy.

Cynthia L. Harden, MD, received her medical degree at the University of Wisconsin and trained in internal medicine at Mount Sinai St. Luke's Hospital and neurology at Mount Sinai Hospital in New York City and in clinical neurophysiology at Albert Einstein College of Medicine in the Bronx. She served most of her career at the Weill Cornell College of Medicine, where she became Professor of Neurology. For the American Academy of Neurology, she serves as Chair of the Guideline Development, Dissemination and Implementation Subcommittee of the American Academy of Neurology. In 2016, she was elected to chair the Epilepsy Section for a 2-year term. She is currently Director of Clinical Epilepsy Services for the Mount Sinai Health System in New York City.

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Augustina O. Charway-Felli, MD, PhD, is a neurologist at the Medical Division of the Military Hospital in Accra, Ghana. She graduated from the IM Sechenov Moscow Medical Academy (now named the I.M. Sechenov First Moscow State Medical University), where she completed a doctorate program in neurology and neurogeriatrics. She returned to her home country of Ghana in 2007 to become 1 of only 2 practicing neurologists at that time. There are now 6 practicing neurologists, but Dr. Charway-Felli remains the only woman. Dr. Charway-Felli is the 2nd Vice President of the Ghana chapter of the International League against Epilepsy (Ghana Epilepsy Society) and 2nd vice president of the Neurological Society of Ghana. The African Academy of Neurology was created in 2015 and Dr. Charway-Felli was elected Secretary-General. Dr. Charway-Felli specializes in cognitive and behavioral neurology and functional neurologic disorders. With the huge deficit of neurologists in Ghana, she mostly practices general adult neurology, and occasionally even child neurology.

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