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Pregnancy and epilepsy—when you're managing both

When a patient with epilepsy is pregnant or planning for pregnancy, you face the challenge of balancing the benefits and teratogenic risks of her antiseizure medication. Here's help.

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PRACTICE RECOMMENDATIONS

› *Use the dose of antiepileptic drug (AED) at which the patient is seizure-free prior to conception as a target level to adjust dosing during pregnancy.* (C)

› *Avoid switching a pregnant patient to an AED that she has not taken before.* (C)

› *Start all women who have epilepsy and are of childbearing age on ≥0.4 mg folic acid daily prior to conception.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

About 500,000 women in the United States suffer from epilepsy and are of childbearing age.[1] For these patients and their physicians, family planning and pregnancy are complex and fraught with risk.

The dilemma: Infants born to women with epilepsy have a 2- to 3-fold risk of congenital malformations compared with those whose mothers do not have epilepsy, mainly related to exposure to antiepileptic drugs (AEDs).[2] Recent studies also suggest that children exposed to AEDs such as valproate, phenobarbital, and phenytoin in utero may have neurocognitive deficits, even when there are no major congenital malformations.[1,3,4]

Yet discontinuing the drugs prior to conception or in early pregnancy is rarely a viable option. In 1 recent prospective study, convulsive seizures during the first trimester (the type and timing of seizure thought to have the most harmful effect on the developing fetus) were associated with malformations in 7.4% of pregnancies.[2] Seizures also increase the risk of both fetal and maternal death, although the extent of that risk is not known.[5]

Ideally, pregnant women with epilepsy should be under the care of both an obstetrician experienced in high-risk pregnancies and a neurologist or an epileptologist. In reality, those who live in areas with limited access to such specialized care or have limited health coverage may be cared for throughout their pregnancy by a family physician. This evidence-based review was developed with this family physician in mind.

Safeguarding mom and fetus starts before pregnancy

Mechanisms by which AEDs cause fetal and embryonic harm remain unclear. Possible causes include drug toxicity, drug-

drug interactions, folic acid deficiency, the effect of suboptimally controlled convulsions, genetic predisposition, enhanced apoptotic neurodegeneration, and alterations in thyroid hormone status, among others.[6-9] Major congenital malformations may occur in a dose-dependent manner, and physicians should aim to use the most effective AED at the lowest effective dose for women of childbearing age.[2]

In reviewing antiseizure therapy for such patients, here are some considerations to keep in mind:

Avoid polytherapy, if possible. Taking multiple AEDs may increase the risk of major congenital malformations, especially when valproate is one of the drugs.[1] Hence, an attempt should be made to switch women with epilepsy who are of childbearing age to monotherapy. Ideally, this should be done a year before planned conception so that good seizure control can be achieved and documented prior to pregnancy.

Avoid high-risk AEDs. Overall, an increased risk of major congenital malformations has been most convincingly found with valproate and phenobarbital.[1] Specific types of malformations have also been linked to certain drugs (**TABLE**). Cardiac malformations are associated with carbamazepine, phenobarbital, and valproate; spina bifida, hypospadias, porencephaly, and other brain anomalies, as well as limb reduction defects, are associated with valproate, particularly at doses >1100 mg/d.[10]

Choose newer agents, whenever possible. The risk of malformations with newer AEDs—including gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate—remains unclear, but preliminary data for monotherapy with these agents suggest a lower teratogenic risk compared with traditional AEDs, such as phenobarbital and valproate.[10]

Initiate folic acid supplementation. Drug-induced folate deficiency has been proposed as a contributing factor in the teratogenicity of AEDs, so diligence is essential in ensuring that patients who have epilepsy and are of childbearing age take folic acid.[11] Studies have demonstrated a significant reduction in spontaneous abortion in women who are receiving AED therapy and taking folic acid supplements, and the benefits of folic acid have been found to be especially notable for women taking valproate.[12]

Folic acid supplementation, of course, is important for all women of childbearing age. At a dose of 0.8 mg/d, folate has been shown to reduce the risk of neural tube and ventricular septal defects in the general population. The American Academy of Neurology/American Epilepsy Society (AAN/AES) Practice Parameters recommend that all women of childbearing age taking AEDs also take folate supplements (0.4-4 mg/d).[13] An optimal dose has not been determined for this patient population, but we routinely recommend 1 mg/d for women with epilepsy of childbearing age and increase the dose to 4 mg/d after conception.

Monotherapy with a newer antiepileptic drug appears to be the safest and best-tolerated option for women of childbearing age, provided adequate seizure control can be obtained.

Switching (or stopping) AEDs before conception

Changes in AEDs are rarely made after conception. Any switches that patients may desire—from a potentially unsafe drug to a "safer" AED, for example—should be considered at least a year prior to planned pregnancy so good seizure control can be achieved before then.

In attempting a change in medication, start by checking the serum drug level of the patient's effective, yet potentially unsafe, antiseizure drug. That allows you to determine the baseline therapeutic drug level and dose at which the patient is seizure-free. Then add the second, safer AED and taper it up to its therapeutic dose, guided by serum drug levels and the manufacturer's recommended titration schedule. Once the new medication has reached the therapeutic serum level, begin titrating the older AED down. If the patient suffers a breakthrough seizure during the cross-taper, we recommend aborting the process and rapidly titrating the first drug back to the predetermined therapeutic level.

What about stopping AED therapy entirely if your patient wants to get pregnant? Stopping AEDs is a clinical decision made by the treating physician in accordance with the patient's wishes on a case-by-case basis, and should be considered only when it is highly likely that seizures will not recur as a result. If the patient has a history of poorly controlled epilepsy despite adequate AED trials, a structural brain lesion, persistently abnormal electroencephalograms, or any other finding that

TABLE

Commonly used antiepileptic drugs: Major teratogenic risks[1,10,19]

AED	FDA pregnancy category*	Associated risks	Recommendations for use during pregnancy
Carbamazepine	C	Cardiac malformations	Lower teratogenic potential compared with phenobarbital and valproate
Gabapentin	C	No MCMs associated with monotherapy	Limited data suggest lower teratogenic risk compared with traditional AEDs†
Lamotrigine	C	No distinctive pattern of MCMs	Limited data suggest lower teratogenic risk compared with traditional AEDs†
Levetiracetam	C	Pyloric stenosis (in polytherapy with lamotrigine); spina bifida (in polytherapy with carbamazepine and valproate)	Limited data suggest lower teratogenic risk compared with traditional AEDs†
Oxcarbazepine	C	Urogenital malformations	Limited data suggest lower teratogenic risk compared with traditional AEDs†
Phenobarbital	D	Cardiac malformations Increases risk of MCMs to at least double that of general population	Best avoided in women of childbearing age
Phenytoin	D	Bradycardia and hypotension; fetal hydantoin syndrome	Best avoided in women of childbearing age
Topiramate	C	Hypospadias; oral clefts	Limited data suggest lower teratogenic risk compared with traditional AEDs†
Valproate	D	Cardiac malformations; hypospadias; limb reduction defects; neural tube defects; porencephaly; spina bifida Increases risk of MCMs to at least double that of general population	Best avoided in women of childbearing age

AED, antiepileptic drug; FDA, US Food and Drug Administration; MCMs, major congenital malformations.

*Category C indicates that human data are lacking and animal studies were positive OR not done; Category D indicates that human data have shown a teratogenic risk but the benefits may outweigh the risk.

†Traditional AEDs include carbamazepine, phenobarbital, phenytoin, and valproate.

suggests she may have recurrent seizures, explain that the risk of discontinuing the medication is greater than the risk of fetal exposure to AEDs. It is also important to point out that more than 90% of women with epilepsy have normal, healthy children[14]—and that there are other steps to take to mitigate risk.[13]

What to consider in the first trimester

Registries that aim to gather data on the outcomes of a large number of AED-exposed pregnancies are a source of reliable information regarding the risks associated with various antiseizure agents. The primary US-based registry is the AED Pregnancy Registry, available at http://aedpregnancyregistry.org. We recommend that physicians caring for pregnant women with epilepsy encourage them to enroll early on, before any prenatal tests are performed. Explain to your patient that by joining the registry, she will be helping others like her make informed decisions about prenatal care.

Prenatal testing. We also recommend that pregnant women taking AEDs—particularly those on higher-risk drugs such as

valproate—undergo a detailed first trimester ultrasound study between 16 and 20 weeks' gestation. Amniocentesis should be avoided, if possible; if needed, however, amniotic alpha-fetoprotein levels may be determined for additional risk assessment.[15]

Medication changes. Once a woman is pregnant, stopping or switching AEDs requires a higher level of caution and is usually ill advised. We generally avoid medication switches after conception. But if a patient explicitly requests a change to a "safer" agent, we may attempt a cross-taper, as we would before pregnancy. Evidence suggests, however, that it may be too late to avoid the risk for major congenital malformations, which typically develop very early in pregnancy.[1,3]

Avoid untried AEDs. We advise against changing a pregnant woman's seizure medication to an agent she has not tried before, because of the risks of both common adverse effects, such as allergies, and rare idiosyncratic reactions leading to aplastic anemia and Stevens-Johnson syndrome.

More than 90% of women with epilepsy have normal, healthy children.

AED dosing throughout pregnancy

When seizures are well controlled prior to conception, they usually remain controlled during pregnancy, although both increases and decreases in seizure frequency have been reported.[16] Seizure exacerbations are usually due to decreased AED levels; this may be the result of decreased plasma protein binding, decreased albumin concentration, or increased drug clearance,[16] although stress, sleep deprivation, and noncompliance may be contributing factors, as well. The changes in pharmacokinetics make it imperative that seizure frequency as well as AED levels be carefully monitored throughout pregnancy.

Although detailed information about changes in serum levels of the newer AEDs during pregnancy is not available, it can be assumed that they will decline somewhat even if the dose remains the same. Carbamazepine has the least alteration in metabolism during pregnancy,[17] while a widely disparate effect on lamotrigine metabolism during pregnancy has been noted. In some women, serum levels of lamotrigine have been shown to decrease by as much as 60% to 90% due to induction of UDP-glucuronosyltransferase (UGT) enzymes,[18] the drug's main metabolic enzymes. Increased clearance of lamotrigine typically occurs within the first several weeks of pregnancy and returns to baseline within 2 weeks after birth.

As a result, incremental dosing of lamotrigine is usually required early in the pregnancy. In some cases, dramatic increases—several multiples of the preconception dose—may be needed, followed by a rapid decrease after delivery.[18]

Monitoring drug levels

Our approach to monitoring AED levels in a pregnant woman with epilepsy includes the following:

- Check levels at baseline—prior to conception, whenever possible—and monthly throughout the pregnancy, with more frequent checks for women with recurrent seizures and those taking lamotrigine.
- Use the dose at which the patient was seizure-free prior to conception as a target level during pregnancy.
- Adjust the dose as needed to maintain the preconception serum drug level.

Drug-specific considerations. As phenytoin and valproate are highly protein-bound, we follow free levels during pregnancy rather than total levels alone. (If your facility is not equipped to track free drug levels, it is important to realize that total levels of these AEDs may not accurately reflect the drug level.) If your patient is taking phenytoin and you're unable to obtain this information, you can use the patient's albumin level and the total phenytoin level to estimate the free level of the drug with the following formula:

Free phenytoin = measured level/[(0.2 × albumin level) + 0.1].

Provide vitamin K augmentation late in pregnancy. In addition to routinely prescribing 4 mg/d folic acid for pregnant women with epilepsy, we recommend oral augmentation of vitamin K as another protective measure.

AEDs that induce hepatic CYP enzymes also induce vitamin K metabolism, thereby reducing the effectiveness of vitamin K-dependent clotting factors and predisposing newborns to hemorrhagic disease.[13] It remains unclear whether only women who

are taking CYP enzyme-inducing AEDs or all women taking AEDs should receive oral vitamin K supplementation in the last few weeks of pregnancy. We recommend oral vitamin K supplementation for all pregnant women with epilepsy (phytonadione 10 mg/d) starting at 36 weeks' gestation and continuing until delivery despite the lack of a proven benefit because it is safe and carries little, if any, risk.

An intramuscular injection of 1 mg vitamin K is generally given to all newborns—regardless of whether the mother has epilepsy and takes AEDs—to prevent hemorrhagic disease.[13]

Should women taking AEDs breastfeed?

The advantages of breastfeeding are largely undisputed, but women being treated with AEDs are generally concerned about the possibility of contaminated breast milk. While antiepileptic agents such as gabapentin, lamotrigine, levetiracetam, and topiramate are excreted in breast milk in potentially clinically important amounts, no short-term adverse effects have been observed in nursing infants of women being treated with AEDs.[13] Little information is available regarding long-term effects, and the AAN and AES state that further study is needed. Nonetheless, breastfeeding is generally believed to be a relatively safe option for patients with epilepsy who are being treated with AEDs, and is not contraindicated by the AAN/AES guidelines.[13]

Indeed, pregnancy itself is relatively safe for women with epilepsy. When you're involved in their care, your awareness of the teratogenicity of various AEDs, the factors to consider in managing epilepsy and pregnancy, and the steps to take to mitigate risk will help you maximize the chance of a positive outcome. JFP

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During pregnancy, changes in pharmacokinetics may affect dosing requirements, and serum levels of antiepileptic drugs should be monitored at least monthly.

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