

# Pregnancy and epilepsy— managing both, in one patient

↘ When a woman who has epilepsy is pregnant or planning for pregnancy, you face the challenge of balancing the benefits and teratogenic risks of her antiseizure medication. Here is help.

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

## The dilemma

Infants born to women who have epilepsy have a twofold to threefold increased risk of congenital malformations, compared with infants born to women who do not have the disorder. The increased risk is mainly related to exposure to antiepileptic drugs (AEDs).<sup>2</sup> 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.<sup>1,3,4</sup>

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*Dr. Sethi and Ms. Wasterlain report no relevant financial relationships. Dr. Harden reports that she receives research support from Forest Pharmaceuticals; serves as a consultant to H. Lundbeck A/S, Novartis, Sepracor Inc., and UCB; and is a speaker for GlaxoSmithKline, H. Lundbeck A/S, and UCB.*

Yet, discontinuing the drugs prior to conception or in early pregnancy is rarely a viable option. In one 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.<sup>2</sup> Seizures also increase the risk of both fetal and maternal death, although the extent of that risk is unknown.<sup>5</sup>

## Practice recommendations

- If feasible, women with epilepsy who are of childbearing age and taking phenobarbital, valproate, or topiramate should be switched to a safer antiepileptic drug (AED), such as lamotrigine, prior to pregnancy.
- Avoid topiramate in women with epilepsy of childbearing age. New human data show an increased risk of oral clefts, and the FDA recently placed topiramate in Pregnancy Category D.
- Avoid switching a pregnant patient to an AED that she has not taken before.
- Use the dosage of AED at which the patient is seizure-free prior to conception as a target level to adjust dosing during pregnancy.
- Start all women who have epilepsy and are of childbearing age on  $\geq 0.4$  mg folic acid daily prior to conception.

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## Commonly used antiepileptic drugs and their major teratogenic risks

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

\* Traditional antiepileptic drugs include carbamazepine, phenobarbital, phenytoin, and valproate.

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

### Safeguarding mother 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, suboptimally

controlled convulsions, genetic predisposition, enhanced apoptotic neurodegeneration, and alterations in thyroid hormone status, among others.<sup>6-9</sup> 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.<sup>2</sup> A good medical practice is to avoid valproate altogether if possible.

In reviewing antiseizure therapy for such patients, here are some considerations: **Avoid polytherapy, if possible.** Taking multiple AEDs may increase the risk of major congenital malformation, especially when valproate is one of the drugs.<sup>1</sup> Therefore, 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 conception is planned 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 demonstrated with the agents valproate and phenobarbital.<sup>1</sup> Specific types of malformation have also been linked to certain drugs (TABLE, page 19). Cardiac malformations are associated with carbamazepine, phenobarbital, and valproate. Spina bifida, hypospadias, pencephaly, and other brain anomalies, as well as limb reduction defects, are associated with valproate, particularly at dosages exceeding 1,100 mg/day.<sup>10</sup>

**Choose newer agents whenever possible.** The risk of malformation 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.<sup>10</sup>

**Initiate folic acid supplementation.** Drug-induced folate deficiency has been proposed as a contributing factor in the teratogenicity of AEDs, so diligence is essential to ensure that patients who have epilepsy and are of childbearing age take folic acid.<sup>11</sup> 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.<sup>12</sup>

Folic acid supplementation, of course, is important for all women of childbearing age. At a dosage of 0.8 mg/day, 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 who are taking an AED also take a folate supplement (0.4–4.0 mg/day).<sup>13</sup> An optimal dosage has not been determined for this population; we routinely recommend 1 mg/day for women with epilepsy who are of childbearing age; we increase the dosage to 4 mg/day after conception.

### Switching (or stopping) AEDs before conception

Changes in AEDs are rarely made after conception. Any switches that a patient may desire—from a potentially unsafe drug to a “safer” AED, for example—should be considered at least a year before she plans to conceive so that good seizure control can be achieved by then.

Begin by checking the serum drug level of the patient’s effective, yet potentially unsafe, antiseizure drug. That will allow you to determine the baseline therapeutic drug level and dosage at which the patient is seizure-free. Then add the second, safer AED and taper it up to its therapeutic dosage, 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.

### Is discontinuation of AED therapy advisable if a patient wants to become pregnant?

Stopping an AED 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

#### FAST TRACK

Any switch of a patient from a potentially unsafe antiepileptic drug to a “safer” agent should be done at least 1 year before she plans to conceive

#### >> More on epilepsy and pregnancy

Read why it’s important to screen rigorously for malformations and when cesarean delivery may be preferable to vaginal birth. See “Guidelines confirm safety of pregnancy in women who have epilepsy—with caveats,” by Janelle Yates (September 2009)

You can find the article in the archive at [obgmanagement.com](http://obgmanagement.com)

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, or if she has a structural brain lesion, persistently abnormal electroencephalograms, or any other finding that suggests that she may have recurrent seizures, explain that the risk of discontinuing the medicine is greater than the risk of fetal exposure to an AED. It is also important to point out that more than 90% of women who have epilepsy have normal, healthy children<sup>14</sup>—and that there are other steps to take to mitigate risk.<sup>13</sup>

### What to consider during 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 (<http://aedpregnancyregistry.org>). We recommend that physicians caring for pregnant women who have epilepsy encourage them to enroll early, 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 who are taking an AED—particularly those taking a higher-risk drug such as valproate—undergo a detailed first-trimester ultrasonographic 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.<sup>15</sup>

**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 of major congenital malformations, which typically develop very early in pregnancy.<sup>1,3</sup>

**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.

### 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.<sup>16</sup> 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,<sup>16</sup> 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,<sup>17</sup> whereas 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,<sup>18</sup> 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



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pregnancy. In some cases, dramatic increases—several multiples of the preconception dosage—may be needed, followed by a rapid decrease after delivery.<sup>18</sup>

### Monitoring drug levels

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

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

**Drug-specific considerations.** Because 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 corrected level of the drug with the following formula:

$$\text{Corrected phenytoin} = \frac{\text{measured total level}}{[(0.2 \times \text{albumin level}) + 0.1]}$$

**Provide vitamin K augmentation late in pregnancy.** In addition to routinely prescribing 4 mg/day of folic acid for pregnant women who have 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.<sup>13</sup> It remains unclear whether only women who are taking CYP enzyme-inducing AEDs or

## INTEGRATING EVIDENCE AND EXPERIENCE

### For the developing fetus, newer drugs are safer

Newer-generation antiepileptic drugs (AEDs), which include **lamotrigine, oxcarbazepine, topiramate, gabapentin, and levetiracetam**, are not associated with an increased risk of major birth defects in the first year of life when they are used during the first trimester of pregnancy, according to a new cohort study from Denmark. The study, published in the May 18, 2011, issue of *JAMA*, includes data on 837,795 live-born infants in Denmark from January 1996 through September 2008. Individual-level information on the AEDs dispensed to mothers, the diagnosis of any birth defects, and potential confounders were ascertained from nationwide health registries.

Of the live births included in the study, 19,960 involved infants who had a diagnosis of a major birth defect (2.4%) during the first year of life. Among 1,532 pregnancies exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam at any time during the first trimester, 49 infants (3.2%) had a major birth defect. In comparison, 19,911 infants (2.4%) of 836,263 unexposed pregnancies had a major birth defect. After adjustment for various variables, Ditte Molgaard-Nielsen, MSc, and Anders Hviid, MSc, DrMedSci, found **no increased risk of major birth defects associated with use of the newer-generation AEDs**, though exposure to gabapentin and levetiracetam during the first trimester was uncommon.

“Our study, to our knowledge, is the largest analytic cohort study on this topic and provides comprehensive safety information on a class of drugs commonly used during pregnancy,” write Molgaard-Nielsen and Hviid. “The use of lamotrigine and oxcarbazepine during the first trimester was not associated with moderate or greater risks of major birth defects like the older-generation antiepileptic drugs, but our study cannot exclude a minor excess in risk of major birth defects or risks of specific birth defects. Topiramate, gabapentin, and levetiracetam do not appear to be major teratogens, but our study cannot exclude minor to moderate risks of major birth defects,” the authors conclude.

### Topiramate remains a category D drug

The findings of this cohort study do not change the fact that topiramate was recently designated as a Pregnancy Category D drug. The US Food and Drug Administration issued an alert on March 4, 2011, notifying health-care professionals and patients that the drug's category had changed from C to D because of new evidence of an increased risk of oral clefts in infants exposed to the agent in utero. Pregnancy Category D means that there is positive evidence of human fetal risk based on human data but the potential benefits from use of the drug in pregnant women may be acceptable in certain situations despite its risks.

—Janelle Yates, Senior Editor

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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 who have epilepsy (phytonadione 10 mg/day), 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 of vitamin K is generally given to all newborns—regardless of whether the mother has epilepsy and takes an AED—to prevent hemorrhagic disease.<sup>13</sup>

### Should women taking an AED breastfeed?

The advantages of breastfeeding are largely undisputed, but women being treated with an AED are generally concerned about the possibility of contaminated breast milk. Although 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 an AED.<sup>13</sup> 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 who have epilepsy who are being treated with an AED, and it is not contraindicated by AAN/AES guidelines.<sup>13</sup>

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

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**Breastfeeding is generally believed to be a relatively safe option for women who have epilepsy who are being treated with an antiepileptic drug**