

# Guidelines confirm safety of pregnancy in women who have epilepsy – with caveats

➔ Otherwise healthy women can expect an uneventful pregnancy and delivery, provided they avoid valproate, seizures, and smoking

**IN THIS ARTICLE**

**Quick facts about epilepsy in women**  
page 29

**Guidelines spell out drug concerns and other measures to protect the fetus**  
page 30

**Is cesarean delivery warranted?**  
page 32

**F**irst-trimester exposure to the antiepileptic drug valproate increases the risk of major congenital malformation, particularly neural tube defects and facial clefts, according to recent guidelines developed by the American Academy of Neurology (AAN) and the American Epilepsy Society (AES).<sup>1-3</sup> The guidelines recommend that women who have epilepsy avoid taking valproate during pregnancy.

“Good evidence shows that valproate is linked to an increased risk for fetal malformations and decreased thinking skills in children, whether used by itself or with other medications,” said lead guideline author Cynthia Harden, MD, director of the Epilepsy Division at the University of Miami’s Miller School of Medicine and member of the AAN.

The guidelines also suggest that, if possible, women who have epilepsy avoid taking more than one epilepsy drug during pregnancy because the use of multiple anti-seizure medications increases the risk of birth defects.

In addition, the guidelines recommend that physicians avoid prescribing the epilepsy drugs phenytoin and phenobarbital during pregnancy. When a fetus is exposed to one of these drugs, cognitive development may be impaired.

## Safe pregnancy is likely – if no seizures occur

Aside from the risks known to be associated with valproate, phenytoin, phenobarbital, and polytherapy, pregnancy in women who have well-controlled epilepsy appears to be relatively safe.

**Janelle Yates**  
Senior Editor

**>> SHARE YOUR COMMENTS**

Do you consult with a neurologist when a patient who has epilepsy becomes pregnant? Can you offer any pearls about the process? Let us know:

E-MAIL [obg@dowdenhealth.com](mailto:obg@dowdenhealth.com)  
FAX 201-391-2778

“Overall, what we found should be very reassuring to every woman with epilepsy planning to become pregnant,” said Harden.

“These guidelines show that women with epilepsy are not at a substantially increased risk of having a cesarean section, late-pregnancy bleeding, or premature contractions or premature labor and delivery. Also, if a woman is seizure-free 9 months before she becomes pregnant, it’s likely that she will not have any seizures during the pregnancy.”

However, a just-published study suggests that the presence of seizures during pregnancy confers some degree of risk, according to data from Yi-Hua Chen, PhD, and colleagues, of Taipei Medical University and General Cathay Hospital in Taiwan.<sup>4</sup>

Chen and associates performed a retrospective cross-sectional study that linked two nationwide population-based data sets from Taiwan. The study focused on 1,016 women who had epilepsy and who delivered singleton infants from 2001 to 2003; these women had been diagnosed with epilepsy within 2 years prior to their index delivery. Women who had epilepsy were further stratified into two groups: those who did and those who did not have seizures during pregnancy. They were compared with 8,128 women who had no chronic disease.

Women who experienced seizures during pregnancy were more likely to give birth to preterm, small, or low-birthweight babies than were women who did not have epilepsy. In addition, women who experienced seizures during pregnancy were more likely to give birth to a small-for-gestational-age infant than were women who had epilepsy but who did not have seizures.

Some previous studies had reported a link between adverse pregnancy outcomes and a mother’s epilepsy, but others found no association, Chen and colleagues observed.

“Our study further illuminates these conflicting data to suggest that it is the seizures themselves that seem to contribute greatly to the increased risk of infants being delivered preterm, of low birthweight, and small for gestational age. For women who remained seizure-free throughout pregnancy,

## Quick facts about epilepsy in women

- It is estimated that approximately 500,000 women of childbearing age in the United States have epilepsy, and that 3 to 5 of every 1,000 births are to women who have epilepsy.
- Most people who have epilepsy have well-controlled seizures and are otherwise healthy.
- The birth rate in women who have epilepsy is slightly lower than it is in women who do not have the disease.<sup>10</sup>
- Most women who have epilepsy have uneventful pregnancies and deliver healthy infants with no complications.<sup>11</sup>
- Epilepsy can be associated with reproductive endocrine disorders, including polycystic ovary syndrome, hypothalamic amenorrhea, or functional hyperprolactinemia, possibly through the effects of antiepileptic drugs.<sup>12</sup>
- The children of women who have idiopathic epilepsy have a slightly elevated risk (<5%) of developing it themselves. The risk is even lower if the mother has symptomatic epilepsy. If both parents have idiopathic epilepsy, the risk that their child will have it, too, rises to 20% to 30%.<sup>13</sup>

null or mild risk was identified, compared with unaffected women,” they wrote.

## As a safeguard, measure blood levels of antiseizure drugs

The guidelines from the AAN and AES recommend that pregnant women who have epilepsy consider having their blood tested regularly.

“Levels of seizure medications in the blood tend to drop during pregnancy, so checking these levels and adjusting the medication doses should help to keep the levels in the effective range and the pregnant woman seizure-free,” said Harden.

Antiepileptic drugs should be administered at the lowest dosage and lowest plasma level that protects against tonic-clonic seizures and other complex partial seizures.<sup>5</sup>



**Levels of anti-epileptic drugs tend to drop during pregnancy, so a dosage adjustment may be necessary to prevent seizures**

CONTINUED ON PAGE 30

## Guidelines spell out drug concerns and other measures to protect the fetus

Here is a summary of the main recommendations in the guidelines from the American Academy of Neurology and American Epilepsy Society:

### Avoid certain drugs; discourage smoking

- Avoid first-trimester exposure to the antiepileptic drug valproate because of its link to an increased risk of fetal malformation and cognitive impairment in children. Also avoid epilepsy drug polytherapy during the first trimester.
- Besides avoiding valproate and antiepileptic drug polytherapy during the first trimester, women who have epilepsy should avoid these regimens throughout pregnancy to prevent adverse cognitive outcomes in the infant.
- Avoid prescribing phenytoin and phenobarbital during pregnancy.
- Women who take antiepileptic drugs are probably at increased risk of delivering a small-for-gestational-age baby and, possibly, delivering a newborn with an Apgar score below 7 at 1 minute.
- Women who have epilepsy and who smoke may increase the risk that they will develop premature contractions, premature labor, and premature delivery.

### Monitor levels of some drugs

- Monitor levels of lamotrigine, carbamazepine, and phenytoin during pregnancy. Also monitor levels of levetiracetam and oxcarbazepine (a monohydroxy derivative). Blood levels of antiepileptic drugs tend to drop during pregnancy, and the dosage may need to be adjusted.

### Seizure-free pregnancy is possible

- Counsel women who have epilepsy that remaining free from seizures for at least 9

months before pregnancy greatly increases the likelihood that they will remain seizure-free during pregnancy.

### Folic acid may be beneficial

- Consider giving women who have epilepsy at least 0.4 mg of folic acid daily before they become pregnant, as it appears likely to lower the risk of major congenital malformation. It is unclear whether a higher daily dosage offers greater protective benefits.

### Counsel the mother about breastfeeding concerns

- Women who have epilepsy and who choose to breastfeed should be counseled that primidone and levetiracetam probably pass into breast milk in significant amounts. In addition, gabapentin, lamotrigine, and topiramate may pass into breast milk in significant amounts. In contrast, valproate, phenobarbital, phenytoin, and carbamazepine probably do not pass into breast milk in clinically important amounts.

### Guidelines were based on a review of the literature

The guidelines were developed after a review of all scientific studies available on each topic and were published in the online issue of the journal *Epilepsia*.<sup>1-3</sup> Their development was supported in part by the Milken Family Foundation.

“For too long, women living with epilepsy have feared the added risk of premature birth and other consequences of both their epilepsy and their medications,” said Howard R. Soule, PhD, chief science officer for the Milken Family Foundation. “The results of this project will help relieve the worries of these women and their families.”

## Do not withdraw antiepileptic drugs during pregnancy

Some physicians attempt to discontinue an antiepileptic drug when a woman has gone 2 years without experiencing a seizure.<sup>5</sup> In this scenario, the likelihood that seizures will recur within 6 and 12 months is 12%

and 32%, respectively.<sup>6</sup> Because of the risk that seizures will recur, and the increased likelihood of adverse outcomes associated with seizures during pregnancy, antiepileptic medication should not be discontinued during gestation.

Nor should a woman attempt to transi-



For more on the AAN/AES guidelines on epilepsy and pregnancy, visit the AAN Web site at <http://www.aan.com/go/practice/guidelines>

tion from one antiepileptic drug to another during pregnancy solely for the purpose of reducing teratogenicity.<sup>5</sup> Doing so could precipitate seizures and exposes the fetus to the potentially hazardous effects of an additional antiseizure medication during a critical period. Moreover, there may be no advantage associated with switching drugs once a pregnancy has been established.<sup>7</sup>

### Screen for malformations rigorously

Comprehensive screening for fetal anomalies early in the pregnancy is recommended for two main reasons:

- If a malformation is identified, the mother has the option of terminating the pregnancy
- Even if the patient decides not to terminate a gestation in which fetal anomaly has been identified, the information may help the practitioner determine the best mode and place of delivery.

### Cesarean delivery may be warranted if the mother has had recent seizures

Although most women who have epilepsy can expect to have a normal vaginal delivery,

elective cesarean should be considered if the mother has experienced frequent seizures during the third trimester, or if she has a history of stress-related status epilepticus.<sup>5</sup>

Tonic-clonic seizures occur during labor in 1% to 2% of women who have epilepsy, and in an additional 1% to 2% of women in the 24 hours immediately following delivery.

Plasma levels of antiepileptic medication should be monitored during the third trimester and delivery to ensure that the medication is given in adequate strength to prevent seizures. In addition, the patient should be counseled about the importance of taking her medication consistently during this period.<sup>5</sup>

If the patient experiences a seizure during labor and delivery, treat her promptly with an intravenous benzodiazepine, preferably lorazepam.<sup>8</sup> However, be aware that phenobarbital, primidone, and benzodiazepines remain in neonatal plasma for several days after delivery and may cause sedation or neonatal withdrawal syndrome.<sup>9</sup>

Do not give magnesium sulfate for epileptic seizures unless the seizures first appear during the third trimester or immediate postpartum period and could be associated with eclampsia. In such cases, treat the eclampsia and evaluate the patient for other potential causes of the seizures.<sup>5</sup>

#### References

1. Harden CL, Hopp J, Ting TY, et al. Management issues for women with epilepsy—focus on pregnancy (evidence-based review): I. Obstetrical complications and change in seizure frequency: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1229–1236.
2. Harden CL, Meador KJ, Pennell PB, et al. Management issues for women with epilepsy—focus on pregnancy (evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1237–1246.
3. Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy—focus on pregnancy (evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50:1247–1255.
4. Chen YH, Chiou HY, Lin HC, Lin HL. Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. *Arch Neurol*. 2009;66:979–984.
5. Schachter SC. Management of epilepsy and pregnancy. ©2009.

UpToDate.com. Available at: [www.uptodate.com/patients/content/topic.do?topicKey=-JqqkRi44op3f4Y](http://www.uptodate.com/patients/content/topic.do?topicKey=-JqqkRi44op3f4Y). Accessed Aug. 17, 2009.

6. EURAP study group. Seizure control and treatment in pregnancy: observations from the EURAP epilepsy pregnancy registry. *Neurology*. 2006;66:354–360.
7. Practice parameter: management issues for women with epilepsy (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 1998;51:944–948.
8. Yerby MS. Problems and management of the pregnant woman with epilepsy. *Epilepsia*. 1987;28 Suppl 3:S29–S36.
9. Kuhn W, Koch S, Helge H, Nau H. Primidone and phenobarbital during lactation period in epileptic women: total and free drug serum levels in the nursed infants and their effects on neonatal behavior. *Dev Pharmacol Ther*. 1988;11:147–154.
10. Artama M, Isojarvi JI, Raitanen J, Auvinen A. Birth rate among patients with epilepsy: a nationwide population-based cohort study in Finland. *Am J Epidemiol*. 2004;159:1057–1063.
11. Crawford PM. Managing epilepsy in women of childbearing age. *Drug Saf*. 2009;32:293–307.
12. Bauer J, Cooper-Mahkorn D. Reproductive dysfunction in women with epilepsy: menstrual cycle abnormalities, fertility, and polycystic ovary syndrome. *Int Rev Neurobiol*. 2008;83:135–155.
13. Dam M. Is epilepsy hereditary? Available at: <http://www.epilepsy.dk/handbook/hereditary-uk.asp>. Accessed Aug. 18, 2009.



**Tonic-clonic seizures occur during labor in 1% to 2% of women who have epilepsy, and in an additional 1% to 2% of women in the 24 hours immediately following delivery**