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Optimizing outcomes in pregnant women with epilepsy

■ ABSTRACT

Women with epilepsy are more likely to have maternal and fetal complications during pregnancy. Risks can be minimized with preconception planning, careful obstetric care, and close postpartum follow-up.

■ KEY POINTS

Epilepsy is not a contraindication to pregnancy or breastfeeding.

Antiepileptic therapy should be based on optimum seizure control, using monotherapy if possible.

Valproic acid, used alone or combined with other drugs, has a high rate of teratogenicity.

Lamotrigine, used alone, has a safe risk profile, but its serum concentration needs to be monitored monthly during pregnancy to ensure that therapeutic levels are maintained.

To prevent hemorrhagic disease of the newborn, pregnant women should take vitamin K (10 mg/day orally) during the last month of pregnancy, and newborns should be given 1 mg intramuscularly at birth.

Women should begin folic acid supplementation (≥ 0.4 mg/day) before pregnancy to reduce the risk of neural tube defects.

WOMEN WITH EPILEPSY face special challenges during pregnancy: seizures can lead to maternal and neonatal complications, but antiepileptic medications are often teratogenic.

This article discusses the problems women with epilepsy face during pregnancy and management strategies recommended by the American Academy of Neurology, the American Epilepsy Society, the Epilepsy Foundation of America, the American College of Obstetrics and Gynecology, and the Child Neurology Society.

■ CARE BEFORE PREGNANCY

Women with epilepsy can be reassured that having epilepsy should not prevent them from having children. About 1 million women with epilepsy in the United States are of childbearing age, and about 20,000 babies are born to women with epilepsy each year.¹

Despite the increased risk of maternal and fetal complications, around 90% of pregnant women with epilepsy deliver a healthy newborn.^{2,3}

Close medical care, however, is essential (TABLE 1). A multidisciplinary approach is recommended, involving a patient's primary care physician, an obstetrician who specializes in high-risk pregnancies, and a neurologist.

Antiepileptic drugs may reduce contraception effectiveness

Some antiepileptic drugs reduce the levels of estrogen and progestin needed to block ovulation and at least double the risk of contraception failure (TABLE 2).⁴ They do this by two mechanisms:

- By inducing enzymes (ie, the CYP3A4 component of the hepatic cytochrome

**TABLE 1**

Guidelines for managing pregnant women with epilepsy

Before pregnancy

Strong evidence (class I):

Optimize therapy before conception

Complete antiepileptic drug therapy changes at least 6 months before planned conception, if possible

Begin folic acid supplementation (≥ 0.4 mg/day) during reproductive years and continue throughout pregnancy

During pregnancy

Strong evidence:

Do not change to an alternate antiepileptic drug during pregnancy for the sole purpose of reducing teratogenic risk

Offer patients being treated with carbamazepine, divalproex sodium or valproic acid:

Prenatal testing for serum alpha-fetoprotein (14–16 weeks of gestation)

Level II (structural) ultrasonography (16–20 weeks of gestation)

If appropriate, amniocentesis for amniotic fluid alpha-fetoprotein and acetylcholinesterase levels

Weaker evidence (class III):

Monitor non-protein-bound antiepileptic drug levels. For patients who are stable, measure levels before conception, at the beginning of each trimester, and in the last month of pregnancy.

In addition, measure when clinically indicated (eg, after a breakthrough seizure or if compliance is in doubt)

Prescribe vitamin K 10 mg/day in the last month of pregnancy for women taking enzyme-inducing antiepileptic drugs

After pregnancy

Strong evidence (class I):

Encourage breastfeeding

Monitor breastfed babies for sedation or feeding difficulties

Weaker evidence (class III):

Monitor antiepileptic drug levels through the 8th postpartum week. If an antiepileptic drug dosage was increased during pregnancy, reduce dosage to prepregnancy levels to avoid toxicity

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P450 system), leading to faster clearance of steroid hormones

- By increasing the production of sex hormone-binding globulin.

Patients who desire hormonal contraception and who are taking an enzyme-inducing antiepileptic medication should use a contraceptive formulation containing at least 50 μg of ethinyl estradiol or mestanol,⁵ as well as use a back-up barrier method. Randomized trials of the efficacy of various modes of hormonal contraception in women with epilepsy are needed.

Primary goal is optimal seizure control

The most important goal of therapy, both prenatally and during pregnancy, is to optimally control seizures. The drug selected for a

patient should be determined by the type of seizure she has, using only a single drug if possible.

Many believe that the harm of poorly controlled and frequent generalized motor seizures outweighs the benefits of a less teratogenic but also less effective drug. Generalized tonic-clonic seizures can cause maternal and fetal hypoxia and acidosis^{1,6} and increase the risk of abruptio placenta, miscarriage, blunt trauma, fetal intracranial hemorrhage, and stillbirth.⁷ The fetal consequences of maternal nonconvulsive seizures (such as complex partial seizures) are unclear.

Therapy to control seizures should be optimized well before conception. If a woman with epilepsy plans to become pregnant and is taking a drug with high teratogenic potential,

TABLE 2

Antiepileptic drugs and hormonal contraception

Drugs that may cause contraceptive failure (enzyme-inducing drugs)

Phenobarbital
 Primidone
 Carbamazepine
 Phenytoin
 Oxcarbazepine
 Topiramate

Drugs that do not affect contraception

Valproate
 Felbamate
 Gabapentin
 Lamotrigine
 Vigabatrin
 Tiagabine

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Most women with epilepsy have no change in seizure frequency during pregnancy

attempts can be made to switch her to a drug with a more favorable teratogenic profile. However, these medication changes should be completed at least 6 months before a planned conception, if possible, to avoid fetal damage from a breakthrough seizure.

It is probably not helpful to change a drug during pregnancy with the goal of using a less teratogenic drug, because most of the critical phases of embryologic development occur very early in pregnancy.

Drug therapy may be discontinued in some patients

The American Academy of Neurology recommends as a general rule that discontinuing antiepileptic drugs may be considered in select patients, ie, women who:

- Have been free of seizures for 2 to 5 years
- Have a single seizure type
- Have a normal neurologic examination and normal intelligence
- Have an electroencephalogram that has normalized with treatment.

Some women who have not satisfied all these conditions may also wish to try discontinuing antiepileptic drugs because of concerns about teratogenic effects or interference

with hormonal contraception. Before doing so, the risk of seizures must be carefully considered. The risk of seizure recurrence is greatest within the first 6 months after discontinuing therapy.⁸

Supplement folic acid

All women of childbearing age with epilepsy should take folic acid supplements (≥ 0.4 mg/day), whether or not they are planning a pregnancy in the near future. Unplanned pregnancies in the United States occur in 40% to 50% of women,^{5,9} a rate probably higher in women with epilepsy because antiepileptic drugs interfere with hormonal contraception. About half of planned pregnancies occur without first consulting a health care provider.⁵

Periconceptional folic acid supplementation reduces both primary and secondary risk of neural tube defects in the general population, with a relative risk reduction of from 60% to 85%.^{5,10}

Many issues remain, however: some studies failed to show a protective effect of low-dose folate supplementation (0.4 mg/day) in women with epilepsy using antiepileptic drugs in early pregnancy,¹¹ and recent data suggest an association between maternal autoantibodies against folate receptors and neural tube defects.¹²

The optimal folic acid dose is also unclear: recommended daily doses vary from 0.4 mg (by the US Public Health Service) to 4 mg (by the American College of Obstetrics and Gynecology).¹³

CARE DURING PREGNANCY

Few women have more seizures during pregnancy

Most women with epilepsy have no change in seizure frequency during pregnancy or even develop fewer seizures. Only 15% to 33% have more seizures during pregnancy.^{14,15}

Multiple factors may be responsible for worsening seizure control (TABLE 3).

Antiepileptic drug pharmacokinetics are altered at many levels during pregnancy. Serum drug concentration is reduced by increasing maternal blood volume and other factors, a phenomenon that reaches its nadir at term.¹⁶

TABLE 3

Factors influencing seizure control during pregnancy

Pharmacokinetic

Decrease in serum antiepileptic drug levels, caused by:

- Decreased drug absorption due to delayed gastric emptying, nausea, and vomiting
- Increased volume of distribution (40%–50% increase in plasma volume)
- Increased hepatic metabolism (glucuronidation and P450 system) and reduced concentration of binding proteins
- Increased renal clearance
- Decreased protein binding

Psychological

- Noncompliance with medications
- Increased stress and anxiety

Physiologic

- Sleep deprivation

Hormonal

- Increased estrogen/progesterone ratio
- Increased human chorionic gonadotropin levels in first trimester

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During pregnancy, measure the free fraction of carbamazepine, phenytoin, valproate, phenobarbital

However, seizure frequency increases as early as the first trimester and not necessarily around term, so reduced antiepileptic drug levels only partially explain the phenomenon.

Hormonal changes may also contribute: the ratio of estrogen (which lowers the seizure threshold) to progesterone (which raises it) increases during pregnancy, reaching its peak between weeks 8 and 16.¹⁷

Other factors that may contribute to a lower seizure threshold include stress, anxiety, and sleep deprivation. Also, some women stop therapy because of fear of teratogenic effects.

Monitor drug concentrations

Serum drug concentrations should be monitored throughout pregnancy. Patients who are stable should be tested before conception, at the beginning of each trimester, and during the last month of pregnancy. More frequent monitoring is needed if a patient has breakthrough seizures or if drug compliance is uncertain.⁵

The total concentration of highly protein-bound drugs (eg, carbamazepine, phenytoin, valproate, and phenobarbital) may drop more than the free, biologically active fraction.¹⁸ The free fraction of these drugs, rather than

the total level, should be measured during pregnancy.

The clearance of lamotrigine increases during pregnancy, and levels may drop precipitously. When using this drug, monthly monitoring of levels is prudent.¹⁹

Medications have teratogenic potential

Women should be counseled about the teratogenic potential of antiepileptic therapy: women taking antiepileptic drugs have a higher rate of congenital malformations and minor anomalies in their offspring than does the general population.¹³

Congenital malformations are physical defects that warrant medical or surgical intervention and cause major functional problems. The most common malformations in newborns of mothers with epilepsy are orofacial clefts and congenital heart disease.

Rates of congenital malformations range from 2.3% to 18.6% (combined risk about 7%) in infants of women with epilepsy vs 2% to 3% in the general population.²⁰

Minor anomalies are deviations from the normal morphology, but do not threaten health, impair function, or require intervention. Examples include hypertelorism (widely



spaced eyes), low-set ears, and distal phalangeal hypoplasia. Minor anomalies occur at a rate of up to 30% in the offspring of women with epilepsy taking antiepileptic drugs vs 15% in newborns of matched controls without epilepsy.²¹

Many factors influence the teratogenic potential of antiepileptic drugs.

Higher doses may increase risk. Dose-dependence is well documented for valproate and neural tube defects.² Samren et al²² found that the offspring of mothers taking a high dosage of valproate (> 1,000 mg/day) were 7 times more likely to have neural tube defects than offspring of women taking a lower dosage (≤ 600 mg/day).

Polytherapy increases risk more than monotherapy. Holmes et al²³ found that the rate of congenital malformations was 4.5% in infants exposed to a single antiepileptic drug vs 8.6% in those exposed to two or more. Wide et al²⁴ found that the odds ratio for congenital malformations in an infant exposed to antiepileptic drugs is 1.61 for a single drug and 4.20 for multiple drugs.

Specific drug used. Polypharmacy with certain enzyme-inducing medications may increase the amount of teratogenic metabolites. The Lamotrigine Pregnancy Registry²⁵ found the risk of malformations was 2.7% with polytherapy not including valproate vs 12.5% if valproate was included. Especially harmful combinations included carbamazepine plus phenobarbital plus valproic acid plus or minus phenytoin (58% risk), and phenobarbital plus phenytoin plus primidone.

Certain antiepileptic drugs used individually are also more teratogenic than others (TABLE 4).^{2,13,22,24–31} Lamotrigine has a favorable profile: the Lamotrigine Pregnancy Registry found from a prospective study that it has a 2.9% overall risk of major malformations (confidence interval 1.6%–5.1%),²⁵ comparable to that of the general population.³² No specific malformation has been associated with any medication except for neural tube defects in newborns exposed to valproate (1%–2%) and carbamazepine (0.5%).¹⁰

Other factors may be teratogenic

Seizures may also contribute to teratogenesis. Lindhout et al³³ found that newborns of

TABLE 4

Antiepileptic treatment and incidence of major congenital malformations

DRUG USAGE	INCIDENCE OF MAJOR CONGENITAL MALFORMATIONS*
Any antiepileptic drug	7.86% ²²
Lamotrigine monotherapy	2.1% ²⁶ –2.9% ²⁵
Carbamazepine monotherapy	2.0% ²⁴ –5.2% ²⁷
Phenobarbital monotherapy	4.7% ²⁷ –6.5% ²⁸
Phenytoin monotherapy	3.4% ²⁷ –10.5% ²
Valproic acid monotherapy	8.6% ²⁴ –16.7% ²
Untreated	0.8% ²⁹ –5.0% ²²
General population	1.62%–2.2%. ^{13,30,31}

*Rates are only rough indicators of risk: teratogenesis in pregnancy of women with epilepsy is multifactorial.

women who had seizures of any type during the first trimester had a malformation rate up to 12.3% vs 4% in newborns of women with epilepsy who had no seizures within the same gestational period.

Genetics of certain epilepsy syndromes may also contribute to congenital malformations: some studies found that even untreated women with epilepsy have a higher incidence of malformations than the general population.¹³

However, the association of teratogenesis with either epilepsy or seizure frequency has not been corroborated in more recent studies²³ and remains controversial.

Risk factors specifically associated with neural tube defects include a family history of neural tube defects, a previous pregnancy with neural tube defects (relative risk 10),¹⁰ maternal insulin-dependent diabetes mellitus (relative risk 7.9),³⁴ various nutritional deficiencies and environmental exposures, and high prepregnancy weight (relative risk 1.9 for women weighing 80–89 kg and 4.0 for women weighing > 110 kg vs women weighing 50–59 kg).³⁵

Screening for fetal malformations

All women with epilepsy should be offered prenatal screening for fetal malformations with the following:

Even untreated women with epilepsy may have a higher risk of congenital fetal malformations

TABLE 5

Useful links and resources**www.aedpregnancyregistry.org**

Large antiepileptic-drug pregnancy registry with more than 4,000 women enrolled to date. Useful information for patients and health care providers.

www.otispregnancy.org

Official Web site of the Organization of Teratology Information Services, offering comprehensive and multidisciplinary resources for medical consultation on prenatal exposures.

www.efa.org

The Epilepsy Foundation is dedicated to helping patients with epilepsy participate in all life experiences, and works to prevent, control, and cure epilepsy through research, education, advocacy, and services.

- Maternal serum alpha-fetoprotein testing (14–16 weeks of gestation)
- Structural ultrasonography (16–20 weeks of gestation).
Performed together, these tests have more than 95% sensitivity in detecting open neural tube defects.^{36,37}

Patients with equivocal results should undergo amniocentesis, which increases the sensitivity to more than 99%.³

Cardiac anomalies can also be diagnosed prenatally with detailed sonographic imaging of the fetal heart (18–20 weeks of gestation), which is 85% sensitive.³⁷

The accuracy of ultrasonography for the prenatal diagnosis of cleft lip is less well established. This screening test has inherent ethical implications and may lead to difficult choices if a problem appears to be present.

Vitamin K supplementation

Some case series have found that newborns exposed to enzyme-inducing antiepileptic drugs (ie, phenytoin, phenobarbital, ethosuximide, vigabatrin, primidone, and diazepam) have a higher risk of hemorrhagic disease of the newborn, a condition that has a mortality rate of up to 30%. When it occurs, bleeding usually happens within the first day of life and affects internal organs such as the lungs, abdomen, and brain.³ It is not clear whether the alteration of vitamin K metabolism caused by some antiepileptic drugs is the only mechanism at work.

Prophylactic oral vitamin K supplementation (10 mg/day) is recommended for all women with epilepsy throughout the last month of pregnancy, and 1 mg should be given intramuscularly to the baby at birth.⁵

CARE AFTER BIRTH**Encourage breastfeeding**

New mothers with epilepsy should be encouraged to breastfeed their babies. Most experts believe that the benefits to the mother and baby outweigh the risks.^{3,5,38,39}

All antiepileptic drugs cross into breast milk, but only the free fraction—that which is not bound to maternal serum binding proteins—is available to cross. For drugs that are highly protein-bound, the free fraction is negligible and usually does not produce serious symptoms in the newborn.

For women who take drugs with a relatively large free fraction (eg, levetiracetam, gabapentin, and ethosuximide), breastfeeding is not contraindicated but should be done cautiously. The baby has been exposed to the drugs during pregnancy because of placental transfer. Usually, there is no problem for the baby, and in fact breastfeeding may prevent withdrawal symptoms if the mother has been receiving phenobarbital. There is no absolute contraindication to breastfeeding, and if the mother wants to breastfeed, she should do so and call her pediatrician and neurologist if she thinks there might be a problem, such as excessive sedation in the baby or changes in the levels of activity.

The sedative drugs (phenobarbital, primidone) may be eliminated in the neonate at a reduced rate, resulting in a drug build-up even when the amount ingested through the breast milk is small. Neonates exposed to these drugs should be monitored for sedation.

Only the free fraction of antiepileptic drugs crosses into the breast milk



■ MORE RESEARCH NEEDED

More research is needed to answer questions related to teratogenicity, hormonal contraception, and benefits of folate and vitamin K supplementation, especially in light of the many

new antiepileptic drugs. Pregnant women with epilepsy are strongly encouraged to enroll in the ongoing federal antiepileptic drug pregnancy registry (888-233-2334) to enhance knowledge about the risks and benefits of antiepileptic drugs or to visit the sites listed on TABLE 5. ■

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