Epilepsy in Women

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Epilepsy in women raises special reproductive and general health concerns. Seizure frequency and severity may change at puberty, over the menstrual cycle, with pregnancy, and at menopause. Estrogen is known to increase the risk of seizures, while progesterone has an inhibitory effect. Many antiepileptic drugs induce liver enzymes and decrease oral contraceptive efficacy. Women with epilepsy also have lower fertility rates and are more likely to have anovulatory menstrual cycles, polycystic ovaries, and sexual dysfunction. Irregular menstrual cycles, hirsutism, acne, and obesity should prompt an evaluation for reproductive dysfunction. Children who are born to women with epilepsy are at greater risk of birth defects, in part related to maternal use of antiepileptic drugs. This risk is reduced by using a single antiepileptic drug at the lowest effective dose and by providing preconceptional folic acid supplementation. Breastfeeding is generally thought to be safe for women using antiepileptic medications. (Am Fam Physician 2002;66:1489-94. Copyright© 2002 American Academy of Family Physicians.)

Epilepsy is a group of neurologic conditions characterized by recurrent unprovoked seizures. Approximately 1 percent of the population has epilepsy, making this one of the most common chronic health conditions affecting reproductive-aged women.[1] While the prevalence of epilepsy and approach to treatment are similar for men and women, women with epilepsy are more likely to experience seizure patterns that relate to reproductive cycles and are at risk of reproductive health dysfunction and pregnancy complications.[2] The ovarian steroid hormones estrogen and progesterone alter neuronal excitability and affect the seizure threshold. Epilepsy and antiepileptic drug-related changes in hypothalamic, pituitary, and gonadal hormones have been associated with increased rates of infertility, anovulatory cycles, menstrual irregularity, and polycystic ovaries. Children who are born to women with epilepsy have a higher risk of birth defects, probably related to in-utero exposure to antiepileptic drugs. These hormone-seizure interactions and reproductive health concerns complicate the management of epilepsy in women.

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Hormones and Seizures

Ovarian steroid hormones alter excitability of neurons of the central nervous system.[3-5] Estrogen reduces inhibition at the gamma-aminobutyric acid (GABA-A) receptor, enhances excitation at the glutamate receptor, and increases the number of excitatory neuronal synapses. Progesterone enhances GABA-mediated inhibition, increases GABA synthesis, and increases the number of GABA-A receptors. In animal models of epilepsy, estrogen increases and progesterone decreases the likelihood that a seizure will occur.

Women with epilepsy may experience changes in seizures at puberty, during the menstrual cycle, and at menopause. These seizure patterns are believed to be associated with changes in estrogen and progesterone levels.[3] Although some epilepsy syndromes, such as childhood absence (petit mal) and benign partial epilepsy with centrotemporal spikes (rolandic epilepsy), usually remit at puberty, other epilepsies worsen, especially those that involve partial seizures. Juvenile myoclonic epilepsy is a common epilepsy syndrome occurring primarily in women at puberty and characterized by absence, myoclonic, and tonic-clonic seizures. Juvenile absence epilepsy, characterized by absence

seizures, also arises at puberty and is more common in women. Neither of these epilepsy syndromes is likely to remit. Seizure control may also change during perimenopause because of fluctuations in estrogen and progesterone. Although 30 percent of women experience improvement in seizure control after menopause, another 30 percent describe a worsening in seizure control, many after beginning hormone replacement therapy with unopposed estrogen.[6]

The association between the menstrual cycle and seizures has been extensively investigated. Thirty to 50 percent of women with epilepsy experience catamenial (menstrual cycle-related) seizures.[7] Seizures are more likely to occur near the time of menstrual flow because of progesterone withdrawal and with the estrogen surge at ovulation. For many women, seizures are more random and severe during anovulatory cycles because the ratio of estrogen to progesterone remains high. Observations of hormone-seizure relationships have led to interest in hormonal therapies. While no randomized double-blind placebo controlled trials are available, open trials of high-dose progesterone (provided as natural progesterone suppositories or lozenges or as intramuscular medroxyprogesterone) have shown some success.[8]

Contraceptive Choices

Women receiving a liver enzyme-inducing antiepileptic medication have at least a 6 percent failure rate per year for oral hormonal contraceptive pills.[9] Cytochrome P450-inducing antiepileptic drugs enhance hepatic metabolism of contraceptive steroids and increase binding of steroids to serum proteins. This reduces the concentration of biologically active steroid hormone. Most commonly used oral contraceptives contain 35 mcg or less of estrogenic compounds and may be ineffective in women who take some antiepileptic drugs. Subdermal levonorgestrel implants (Norplant) are also less effective in women receiving enzyme-inducing antiepileptic drugs.[10] Women taking enzyme-inducing antiepileptic drugs should use nonhormonal methods of contraception or receive contraceptives containing 50 mcg or more of the estrogenic component.[2,11] Consideration of antiepileptic drugs that do not induce liver enzymes may also be an option in some patients *(Table 1)*.

Reproductive Functioning

Fertility rates in women with epilepsy are reduced by one to two thirds when compared with their nonepileptic female siblings.[12,13] Lower birth rates may reflect some of the social and psychologic pressures experienced by women with epilepsy. Some women with epilepsy are counseled not to have children because of the fear of transmitting epilepsy, the concern that antiepileptic drugs will cause birth defects, or the belief that seizures will render them unfit parents. Misinformation about epilepsy fuels many of these fears.[14]

In addition to these social pressures, there is a physiologic basis for infertility in women with epilepsy. Up to one third of women with epilepsy have an abnormal menstrual cycle length (less than 23 days or more than 35 days). One third or more of menstrual cycles in women with generalized seizures are anovulatory.[15] Reproductive endocrine disorders in women with epilepsy include disturbances in luteinizing hormone concentration and pulsatile release and abnormalities in

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TABLE 1
Antiepileptic Drug Effects on Oral Contraceptives

Agents that induce liver enzymes and may compromise OC efficacy
Carbamazepine (Tegretol)
Felbamate (Felbatol)
Phenytoin (Dilantin)
Phenobarbital
Primidone (Mysoline)
Oxcarbazepine (Trileptal)
Topiramate (Topamax)
Agents that do not compromise OC efficacy
Gabapentin (Neurontin)
Levetiracetam (Keppra)
Lamotrigine (Lamictal)
Tiagabine (Gabitril)
Valproate (Depakote)
Zonisamide (Zonegran)

OC = oral contraceptive.

prolactin and steroid hormone levels.[16,17] Pituitary hormone abnormalities are probably associated with disruptions in hypothalamic input to the pituitary as a consequence of seizures.

Changes in steroid metabolism and binding related to the use of antiepileptic drugs are another factor that affects ovarian hormone levels and reproductive functioning. Antiepileptic drugs that induce cytochrome P450 enzymes *(Table 1)* enhance steroid metabolism and promote binding to sex hormone binding globulin.[18,19] Valproate (Depakote) inhibits steroid metabolism and is associated with elevations in gonadal testosterone and adrenal dehydroepiandrosterone sulfate (DHEAS) levels.[20]

Polycystic ovaries are described in 20 to 40 percent of women with epilepsy who were evaluated with transvaginal ovarian ultrasound.[20] These women often have an elevated body mass index (more than 25 kg per m^2), hirsutism, abnormal menstrual cycle length, and anovulatory cycles. It is not known whether this condition is the same as polycystic ovary syndrome. Some investigators find that valproate is associated with polycystic ovaries, elevated androgen levels, obesity, and insulin resistance more often than are other antiepileptic drugs.[20] This phenomenon was reversible in a small number of women when their medication was changed from valproate to lamotrigine (Lamictal).[21]

To identify and treat reproductive disorders, women with epilepsy should be asked routinely about commonly occurring problems such as weight gain, abnormal menstrual cycle length or irregularity, mid-cycle spotting, hirsutism, or acne. Suspicion of antiepileptic drug-induced polycystic ovarian syndrome may warrant an endocrine screen, including luteinizing hormone, testosterone and prolactin levels, pelvic examination, and ovarian ultrasound.[11]

Sexual Dysfunction

A reduction in sexual desire is reported in one fourth to one third of women with epilepsy.[22,23] As with infertility, the contribution of the social and psychologic stresses of living with epilepsy may be an important factor in these higher rates of dysfunction. More than one third of women in an outpatient survey reported difficulty with sexual arousal.[22] Another common complaint was painful intercourse because of vaginal dryness and vaginismus. A study[23] of physiologic responses to erotic stimulation found a reduction in vaginal blood flow in women with epilepsy compared with a control group of women without epilepsy.

Dysfunction in sexual arousal is usually best treated with couple's counseling, enhanced foreplay, and vaginal lubrication products. Changing to an alternative antiepileptic drug also may be considered.

Pregnancy

Pregnancy in the woman who has epilepsy raises several concerns, including the risk of

Pregnant women taking antiepileptic medications should receive 10 mg per day of oral vitamin K during the last month of the pregnancy to reduce the risk of neonatal hemorrhage.

more frequent seizures, changes in antiepileptic drug levels because of altered pharmacokinetics and medication compliance, and because of the potential for antiepileptic drug-related teratogenicity.[2,11,24] Women with epilepsy should receive counseling about these potential complications. A few easily instituted therapeutic interventions can reduce the risk of adverse pregnancy and fetal outcomes. Some women may wish to sign up with the national registry that tracks the use of antiepileptic drugs and pregnancy outcomes *(Table 2)*.

Seizure frequency is increased during pregnancy in about one third of women with epilepsy, which is partly caused by poorer medication compliance and changes in antiepileptic drug pharmacokinetics.[25,26] Serum drug levels may be reduced because of increases in volume of distribution, hepatic metabolism, or renal clearance. Protein binding of antiepileptic drugs is reduced because of a drop in serum albumin levels and increased binding by sex steroid hormones, which leads to a relative increase in the nonprotein-bound (free) fraction of drug.[26] For antiepileptic drugs that are highly protein bound, the total antiepileptic concentration may not accurately portray the brain concentration. Therefore, monitoring and adjusting the free level of antiepileptic drug is recommended during pregnancy.[11]

Women with epilepsy have a 4 to 8 percent chance of giving birth to a child with a major malformation, compared with 2 to 4 percent in the general population.[2,11,24,27] Malformations associated with exposure to the older antiepileptic drugs include cleft lip and palate and ventricular septal defect. Neural tube defects are associated with exposure to valproate and carbamazepine (Tegretol) at a frequency of 1 to 2 percent and 0.5 to 1 percent, respectively. Minor congenital anomalies affect 7 to 15 percent of infants exposed to antiepileptic drugs, which represents a twofold increase over that in the general population.[28] These anomalies principally involve the face and digits, including hypertelorism, epicanthal folds, broad nasal bridge, elongated philtrum, distal digital, and nail bed hypoplasia.

There are several potential mechanisms for antiepileptic drug-mediated teratogenesis. Although the maternal trait of epilepsy may predispose neonates to birth defects, a recent study[27] suggests that the risk of birth defects is entirely associated with maternal use of antiepileptic drugs, suggesting that pregnant women using these drugs for indications other than epilepsy are also at risk. The older generation of antiepileptic drugs generate free radical metabolites and induce folic acid deficiency. The risk of teratogenicity is significantly increased in women taking multiple antiepileptic drugs and in those on high doses of antiepileptic medication. The newer generation of antiepileptic drugs is not teratogenic in animals, but

TABLE 2
Resources

Epilepsy Foundation
The Foundation provides information and referral for women with epilepsy. By contacting the Foundation or local affiliates, physicians and lay persons may obtain a series of fact sheets on issues of concern in women with epilepsy.
Telephone: 800-EFA-1000
Web site: www.efa.org
North American Pregnancy Registry
This is a prospective national registry established to identify teratogenic risks of antiepileptic drugs. Pregnant women should contact the registry before they have a diagnostic ultrasound.
Telephone: 888-233-2334

TABLE 3
Guidelines for the Use of Antiepileptic Drugs During Pregnancy

Use the most effective antiepileptic drug in monotherapy and at the lowest possible dose.
If there is a family history of neural tube defects, and there are acceptable treatment alternatives, avoid valproate (Depakote) and carbamazepine (Tegretol).
Monitor the free (nonprotein-bound) fraction of the antiepileptic drug at each trimester, before delivery, and four to eight weeks after delivery.
Adjust the antiepileptic drug dosage according to the nonprotein-bound (free) level.
Provide folate supplementation at a dosage of 0.4 to 4 mg per day before conception and throughout gestation.
Offer prenatal testing with anatomic ultrasound and maternal serum alpha-fetoprotein at 15 to 20 weeks of gestation.
Provide the pregnant woman with vitamin K, 10 mg per day during the last month of gestation.

Information from references 11 and 24.

there is not sufficient reporting in human pregnancy experience to accurately portray risk.

The American Academy of Neurology (AAN) issued a practice parameter advocating single-drug therapy at the lowest possible dose that effectively controls seizures *(Table 3*[11,24]*)*.[2,11] Folic acid supplementation should be provided to all women of childbearing potential. The recommended dosage range is between 0.4 to 4 mg per day,[29] with many neurologists routinely supplementing at 1 mg per day.[11] Suggested prenatal diagnostic testing includes a maternal serum alpha-fetoprotein test at 15 to 20 weeks of gestation and an anatomic ultrasound at 16 to 18 weeks of gestation. This detects neural tube defects with more than 95 percent sensitivity.[11,24] Finally, the AAN recommends that the mother receive 10 mg of oral vitamin K per day during the final month of gestation to reduce the risk of neonatal hemorrhage.[11] This is in addition to the intramuscular vitamin K routinely provided to the neonate at birth.

Breastfeeding is advocated for women with epilepsy, according to the AAN and the American Academy of Pediatrics (AAP).[11] The benefits of breastfeeding are felt to outweigh the potential risk of continued exposure of the neonate and infant to antiepileptic drugs. Antiepileptic drugs cross into breast milk in inverse proportion to their extent of protein binding. Therefore, phenytoin (Dilantin), tiagabine (Gabitril), and valproate, which are all extensively protein bound, have very low concentrations in breast milk. Carbamazepine, phenobarbital, lamotrigine, topiramate (Topamax), and zonisamide (Zonegran) have low to moderate protein binding and can be anticipated to have low to moderate concentrations in breast milk in relation to maternal concentrations. Gabapentin and levetiracetam (Keppra) have no protein binding and therefore have equivalent concentrations in maternal serum and breast milk. It is advised that the breastfed infant of a mother receiving antiepileptic drugs be observed for irritability, poor sleep patterns, or inadequate weight gain.

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