

Women's Issues in Epilepsy

Kirsten Bracht, MD

Women with epilepsy face unique medical concerns when facing treatment with antiepileptic drugs. Medications may affect fertility, sexuality, contraception, pregnancy outcome, and long-term bone health. Menopause and hormone replacement therapy can also be influenced by AED's. An awareness of these issues is essential when caring for women with epilepsy.

Introduction. Women with epilepsy face unique medical concerns when facing treatment with antiepileptic drugs (AED's). Medications may affect fertility, sexuality, contraception, pregnancy outcome, and long-term bone health. Menopause and hormone replacement therapy can also be influenced by AED's. An awareness of these issues is essential when caring for women with epilepsy.

Sexuality. Sexual dysfunction may occur with any AED, although it may be more common with barbiturates. Alterations in hormone binding and metabolism can lead to a decrease in libido and arousal.⁷ Direct effects of AED's on the brain may also play a role. Changing AED's may alleviate a patient's symptoms as medication effects will vary from one individual to another.

Endocrine and Fertility Issues. Fertility rates are often decreased in women with epilepsy. Both AED's and epilepsy itself have been implicated as contributing factors to infertility. Anovulatory menstrual cycles occur up to 30 percent of the time in these women. Endocrine disorders have been described in women with epilepsy even when they have been seizure free. In one study of 50 women with partial seizures of temporal lobe origin, 7 had polycystic ovarian syndrome, 6 had hypogonadotropic hypogonadism, and 7 had hypergonadro-

tropic hypogonadism.⁵ A subsequent investigation found that women with primary generalized seizures showed similar results.¹

Hormonal Contraceptive. Hormonal contraception may be affected by AED's. These include oral contraceptives, levonorgestral IUD, natural family planning, and the "morning after" pill. Some AED's (phenytoin, carbamazepine, phenobarbital, and topiramate) enhance the metabolism of hormones by the cytochrome P450 system, resulting in decreased levels of circulating ethinyl estradiol and progesterin levels. Ethosuximide, oxcarbazepine, and primidone may also impair oral contraceptive efficacy. If unrecognized, this places a woman at risk for unplanned pregnancy. Prescribing an agent with a higher hormone dose could be appropriate in this situation.

AED's which do not affect oral contraceptives include gabapentin, levetiracetam, tiagabine, lamotrigine, and zonisamide. Valproate and felbamate inhibit the cytochrome P450 system with no change or increased hormone levels. If an enzyme-



Dr. Kirsten Bracht is an epileptologist and co-medical director of the CNI Epilepsy Center. She earned her undergraduate degree at Stanford University and attended medical school at the University of Southern California School of Medicine. Dr. Bracht served her neurology residency and received her fellowship training in clinical neurophysiology at USC. She participates in CNI clinical trials, studying promising medications in the treatment of seizures.

Table 2. AED's which reduce oral contraceptive efficacy

- Phenytoin	- Carbamazepine
- Phenobarbital	- Topiramate
- Ethosuxamide	- Oxcarbazepine
- Primidone	

inducing AED must be used, women need to be counseled on these potential risks. In some cases, barrier methods of contraception may be suggested, especially if higher hormone doses are not utilized.

Maternal and Fetal Risks in Pregnancy.

Women with epilepsy who wish to become pregnant should be informed of potential risks to both themselves and their children. It is reassuring to note that over 90 percent of children born to women with epilepsy are normal and healthy.⁸ As with all women, patients need to ensure during pregnancy that they eat a proper diet, get adequate sleep, exercise regularly, maintain a healthy weight, and take supplemental folic acid. Ideally, folic acid should be started prior to conception to try to reduce the occurrence of neural tube defects.

Neural tube defects arise when there is failure of closure of the neural tube at 25 to 27 days gestation. They may be classified by anatomic location (anencephaly versus spina bifida), timing for development (upper versus lower), or syndrome (genetic versus environmental). Risk factors for neural tube defects include maternal age, parity (first or more than three), diabetes, obesity, febrile illness in the first trimester, socioeconomic status (inverse relationship), and employment (chemical exposures). Vitamin supplementation, especially with folic acid, has been shown to reduce congenital abnormalities including neural tube defects.²

Some AED's (carbamazepine, barbiturates, phenytoin, and valproate) interfere with folic acid metabolism. Folic acid supplementation at a minimum of 0.4 mg per day is recommended throughout a women's reproductive years with 2 to 4 mg per day felt to be appropriate by some physicians for women with epilepsy during or when planning pregnancy. A minimum

Table 3. AED's and Pregnancy

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- Monotherapy
 - Lowest dose of AED to control seizures
 - Folic Acid supplementation before conception
 - Vitamin K 10 mg during final month of pregnancy
 - Over 90% of children born to women with epilepsy are normal and healthy
-

of 4 mg per day is usually maintained during pregnancy.

The teratogenicity of AED's has recently been reviewed.⁶ Women on a single AED had a 2.8 fold increase in the occurrence of congenital birth defects, including major malformations, microcephaly, growth retardation, and hypoplasia of the midface and fingers. The risk increased to 4.2 fold when 2 or more AED's were taken. Women with a history of epilepsy who were no longer on AED's showed rates equal to those controls. For women who continue to require treatment with AED's, monotherapy at the lowest dose needed to control seizures is optimal.

Despite the potential risk of teratogenicity, AED's should not be abruptly withdrawn when a pregnancy is discovered. The potential risk of uncontrolled seizures, especially prolonged generalized tonic-clonic seizures, may be much greater than exposure to the AED itself. Results may include fetal trauma, miscarriage, premature labor, fetal distress (bradycardia leading to potential hypoxia), and developmental delay in the child. In fact, by the time a woman confirms her pregnancy, the fetus is often well beyond the critical stage in development (21 to 28 days after conception for neural tube defects (NTD), when a major malformation would occur. Hence, continuing her AED's would pose no additional teratogenic risk, whereas withdrawal certainly could. If a patient is felt to be a candidate for AED withdrawal, this

should ideally be done under medical supervision prior to conception.

Obstetric and Neonatal Issues. Pregnant women with epilepsy are at increased risk for several obstetric and neonatal complications.⁴ Hyperemesis gravidarum, anemia, and premature labor are seen more frequently during pregnancy. The rate of cesarean section is also higher in women with epilepsy. Finally, newborns to mothers with epilepsy on AED's are at risk for a bleeding disorder within 24 hours post-partum. The risk has been found to be up to 7 percent in women taking phenytoin, phenobarbital, or primidone, but is unknown for other AED's. To reduce this risk, women should be given Vitamin K 10 mg daily at 36 weeks gestation for the remainder of their pregnancy.⁸

Bone Health. Evidence continues to emerge that many AED's increase an individual's risk of developing osteoporosis and other bone disorders.³ The prevalence of these conditions has been reported to range from 5 percent to 50 percent, depending upon duration of treatment and specific AED's among other factors. Enzyme-inducing AED's, such as carbamazepine, phenytoin, and phenobarbital appear to alter Vitamin D metabolism. Osteoporosis, osteopenia, and fractures may result.

Bone mineral density testing may be considered as soon as one year after a patient has been on an enzyme-inducing AED. These medications inhibit the 25-hydroxylation of Vitamin D. This leads to a decrease in the active metabolite 1,25 hydroxyvitamin D, which is normally formed in the kidney and allows intestinal absorption of calcium. Valproate, although not an enzyme-inducer, seems to interfere with Vitamin D absorption.⁹ It is possible some of the newer

Table 1. Prevention of bone health

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- Adequate sunlight
 - Weight-bearing exercise
 - Diet rich in calcium
 - Supplemental Vitamin D and calcium
 - Avoidance of alcohol and tobacco
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AED's also affect bone health, however, data on this subject has yet to emerge.

Recommendations should be made to reduce the risk of bone loss through dietary counseling addressing high calcium-containing foods, a regular program of exercise (especially weight-bearing), and the avoidance of alcohol and tobacco-containing products.

Menopause. For some women, seizures seem to decline in frequency with menopause. This tends to occur in women who noted a cyclical relationship to their seizures, such as during menstruation or mid-cycle during ovulation.

One of the major dilemmas facing women during menopause involves whether or not to take hormone replacement therapy (HRT). It is well known that estrogen will increase and progesterone will reduce the likelihood of seizures in animals and in vitro studies. Hormone replacement therapy thus presents several issues. On the one hand, HRT may reduce the risk of osteoporosis; on the other hand, HRT with estrogen alone may potentially increase seizures. Individualized discussions with all health

Table 4. Hormone effects of seizures

Estrogen

- May increase seizures
- Surge with ovulation

Progesterone

- May reduce likelihood of seizures
 - Rapid reduction just before menses
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care providers will best equip a woman to choose what is right for her situation.

Conclusion. Women with epilepsy face unique challenges throughout their lives. From family planning, contraception, pregnancy, menopause, and long-term bone health, there are numerous areas affected by medications prescribed to control seizures. Anti-epileptic drugs influence basic endocrine and metabolic functions. Preparing for and addressing concerns related to these interactions can make a positive influence in a woman's life.

Address comments and questions to:

Kirsten Bracht, MD
701 E. Hampden Avenue
Suite 530
Englewood, CO 80113