Importance of monotherapy in women across the reproductive cycle

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ABSTRACT

Special treatment considerations are warranted in women with epilepsy, particularly those of childbearing age. Treatment guidelines generally recommend the use of antiepileptic drug (AED) monotherapy at the lowest dose possible during pregnancy. The UK Epilepsy and Pregnancy Register reported that the risk for major congenital malformations is higher with AED polytherapy than with monotherapy (6.0% vs 3.7%, respectively) and that valproate carries the highest individual risk. The AEDs that induce hepatic cytochrome CYP450 enzymes carry particular concern both before and after pregnancy. Hepatic enzyme inducers alter steroid metabolism in women receiving oral contraceptives, increase the risk for contraceptive failure, and interfere with calcium absorption and vitamin D metabolism, thus increasing the risk for osteoporosis and fractures. Vitamin K deficiency is another potential consequence of treatment with a hepatic enzyme-inducing AED, increasing the risk for coagulopathy and neonatal intraparenchymal and intracerebral hemorrhage during the first 24 hours of life. Supplemental vitamin K therapy during the last month of pregnancy is warranted. Preconceptional and gestational folate supplementation may also be warranted to prevent neural tube malformation related to AED treatment. Because AED pharmacokinetics may be altered during pregnancy, plasma AED concentrations should be measured before conception and monthly during pregnancy to prevent seizure breakthrough. **NEUROLOGY 2007;69(Suppl 3):S10–S16**

Seizures, antiepileptic drugs (AEDs), and the female reproductive system interact in complex ways during a woman's lifespan, necessitating special attention to the details of seizure management in women with epilepsy (WWE), particularly during the childbearing years.[1–3] Epilepsy affects more than 1.1 million women of childbearing age in the United States.[4] An estimation of 3 to 5 births/1,000 is attributed to WWE each year.[5] In 2003, approximately 4 million babies were born in the United States, of which 20,000 (0.5%) were to WWE. Epilepsy is the most common neurologic disorder that requires continuous treatment during pregnancy.

Seizures and their management affect the likelihood of conception, and once conception has occurred these factors affect the health of both mother and embryo or fetus. Seizures and their management also may affect epileptic women during the postmenopausal years. This article examines the various issues related to management of WWE, with special attention to pregnancy and the use of monotherapy to minimize potential detrimental AED effects on the developing fetus and to simplify pharmacokinetics, reduce drug costs and, possibly, to improve compliance.

EPILEPSY, AEDS, AND FERTILITY: ISSUES BEFORE PREGNANCY Fertility rates in women with treated epilepsy are reduced by more than 25% compared with rates in age-matched WWE.[6] Although this is probably due in part to reduced marriage rates and other social factors, reports indicate that fertility rates are lowered even in married WWE and that the reduced fertility rate is

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Table 1 Effect of AEDs on hepatic CYP450 enzymes

Induce hepatic enzymes; may adversely interact with OCs	Will not adversely interact with OCs	
	Inhibit CYP450 enzymes	No effect on CYP450 enzymes
Carbamazepine	Valproate	Gabapentin
Felbamate	Zonisamide†	Lamotrigine
Oxcarbazepine		Levetiracetam
Phenobarbital		Pregabalin
Phenytoin		Tiagabine‡
Primidone		Vigabatrin
Topiramate*		

OCs = oral contraceptives.
*No interaction up to 200 mg/d; increased steroid metabolism above this dosage.
†Weakly.
‡At low doses.
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only partially explained by the reduced marriage rate.[7,8]

The cause of the reduction in pregnancy and offspring from WWE is probably multifactorial, including neurologic aspects of the disease and, in some cases, contributory elements of AED use. For example, the alteration of central mechanisms for regulating the neuroendocrine system may be involved.[9] In one study, 35% of menstrual cycles were anovulatory in women with temporal lobe epilepsy (TLE) compared with 0% and 8% of cycles in subjects with primarily generalized epilepsy or controls, respectively, suggesting that particular seizure types or loci may be associated with greater likelihood of disturbed neuroendocrine function than others.[10] In this study, anovulatory cycles appeared to be more common in women with TLE treated with AED polytherapy rather than monotherapy, although the difference was not statistically significant.

Along with interference with sex hormones, WWE may face other reproductive health issues, including impaired social functioning leading to decreased sexual activity. In addition, in patients treated with AEDs, the sedative and neurocognitive effects of treatment and the associated disturbances of the neuroendocrine system may decrease libido, thus reducing the likelihood of marriage and/or sexual activity.[11,12]

Antiepileptic drugs may further affect fertility or pregnancy by increasing the risk for polycystic ovary syndrome (PCOS) or by altering the pharmacokinetics of oral contraceptives (OCs). Common signs and symptoms of PCOS include enlargement or other structural abnormalities of the ovary, oligomenorrhea, amenorrhea, infertility due to chronic anovulation, elevated serum androgen levels, and central obesity. Moreover, WWE have a higher incidence of developing multiple ovarian cysts than the general population. Although the relation between AEDs and PCOS is controversial, a number of studies suggest that certain AEDs may increase risk. Much of the attention has focused on valproate, although no cause–effect relation has been firmly established. Nevertheless, some investigators have suggested that menstrual period length and serum androgen levels should probably be monitored in WWE after initiation of valproate therapy.[13]

When certain AEDs are combined with OCs in WWE, the result may be an unwanted or unintended pregnancy. The relative risk for contraceptive failure in women taking OCs and enzyme (CYP450)-inducing AEDs is estimated to be 25 times greater than in nonepileptic women taking OCs alone.[14] The principal mechanism of contraceptive failure is believed to involve induction of hepatic CYP450 enzymes, leading to accelerated metabolism of estrogens to inactive metabolites, thereby decreasing serum estrogen concentrations and allowing subsequent breakthrough ovulation and pregnancy.[15] Enzyme-inducing AEDs may also increase levels of sex hormone-binding globulin (SHBG), leading to decreases in free or biologically active progesterone and estrogen levels and unintended pregnancy.[11,15–17] Table 1[15] provides a list of AEDs and their effects on hepatic CYP450 enzymes. Only enzyme-inducing AEDs increase the risk for OC failure when adjustments are not made to OC dosages. Women taking enzyme-inducing AEDs are recommended to use combined OC formulations that include at least 50 μg ethinyl estradiol or mestranol and to discuss the risk of contraceptive failure with their physician.[5]

Although for the most part OCs do not appear

to affect the efficacy of AEDs, OCs have been reported to significantly decrease plasma levels of lamotrigine and to increase seizure risk.[18] The usual lamotrigine dose should be adjusted when this drug is coadministered with OCs. Drug monitoring is essential to verify therapeutic levels.

ISSUES DURING PREGNANCY Both uncontrolled seizures and AED use during pregnancy may have adverse effects on embryonic or fetal development.[1] Consequently, the goal of epilepsy treatment during pregnancy should be to provide effective seizure control while minimizing adverse effects of AED therapy, which include increased risk for teratogenicity. Repeated seizures during pregnancy are associated with risks to both the mother and fetus and may often be related to inadequate AED use. The benefits of appropriate AED therapy usually outweigh the risks associated with such therapy, which are generally associated with repeated seizures during pregnancy owing to inadequate treatment. The use of monotherapy as opposed to polytherapy has been associated with lower teratogenic risk. This and other matters related to epilepsy and its treatment during pregnancy are discussed in greater detail below.

SEIZURE CONTROL DURING PREGNANCY The effect of pregnancy on seizure risk appears to vary among patients, but a sizeable percentage (17% to 37%) experience an increase in seizure frequency.[19,20] Causes may include hormonal changes as well as lowered plasma levels of AEDs due to pharmacokinetic changes associated with pregnancy or to drug noncompliance.[1,18] Subtherapeutic AED levels are frequently observed in women with increased seizure frequency during pregnancy. In addition, AED absorption may be reduced in some patients due to pregnancy-related nausea and vomiting.[1] Pharmacokinetic changes that occur during pregnancy include increased volume of distribution, increased renal elimination, altered hepatic enzyme activity, and reduced plasma protein concentrations. The net effect for most AEDs is an increase in clearance and a decrease in plasma levels, although these changes may be partially offset by an increase in the free vs the bound fraction owing to reduced production of plasma proteins during pregnancy, particularly for highly protein-bound AEDs.[3,19]

Seizure control is important not only because of the inherent risks to the patient but also because of potential danger to the developing fetus. Although there is no clear evidence that minor or nonconvulsive seizures adversely affect the fetus, generalized tonic–clonic seizures during pregnancy may result in reduced placental blood flow leading to fetal hypoxia and acidosis.[1,3,19] Some studies also have suggested that seizure(s) during the first trimester may be associated with increased risk for malformations[21] and, although rare, status epilepticus during pregnancy is associated with high rates of maternal and fetal mortality. In later pregnancy a maternal seizure may result in a fall that either injures the fetus or precipitates a miscarriage or early labor.[3] For all of these reasons, seizure control is essential in pregnant WWE.

The best approach to seizure management in women planning to become pregnant is to establish effective control before conception. For most women, and particularly those wishing to become pregnant, optimal treatment will include AED monotherapy at the lowest effective dose. As discussed below, AED monotherapy has been associated with a lower risk for teratogenicity than has AED polytherapy. In addition, compliance is likely to be improved with monotherapy. Management of epilepsy in women of childbearing age also should include establishment of therapeutic AED plasma levels,[22] because the AED dosage may need to be modified over the course of a pregnancy to achieve such levels. Guidelines recommend regular monitoring of plasma AED levels in each trimester and shortly after parturition.[5,23] Special attention must be paid to lamotrigine, which exhibits very pronounced increases in clearance during pregnancy that may be associated with increased seizure rate.[24,25] Conversely, shortly after delivery lamotrigine levels once again rise. This indicates that lamotrigine levels should probably be monitored before, during, and after pregnancy, with appropriate dosing adjustments to prevent seizure breakthrough and toxicity. This applies to other AEDs as well.

RISK FOR TERATOGENICITY OR OTHER ADVERSE EFFECTS WITH AEDS Although there is controversy as to whether seizures during pregnancy contribute to teratogenesis, there is little doubt that AEDs do increase risk.[26] This has been firmly established for conventional AEDs, and teratogenic risk appears to be generally similar or lower with certain newer agents, although in most cases the database for newer agents is too limited to draw firm conclusions.

Some of the more common major congenital malformations (MCMs) associated with prenatal AED use affect the cardiovascular system (e.g., atrial or ventricular septal defect and patent ductus arteriosus), the craniofacial structures (cleft lip or palate), the skeleton (e.g., club foot or hip

dislocation), and the CNS (neural tube defects).[2] The syndromes associated with prenatal administration of AEDs vary for the different agents, giving rise to such descriptions as fetal hydrantoin syndrome and fetal valproate syndrome. However, because the syndromes associated with different agents greatly overlap and are often indistinguishable, the more general term "fetal AED syndrome" is commonly used to describe teratogenicity associated with AEDs. In addition to MCMs, prenatal AED use has also been linked with congenital anomalies (more minor deviations that do not threaten health, impair function, or require intervention), neonatal hemorrhage, and developmental delay.

Recognizing the special health issues related to AED treatment during pregnancy, several registries have been established worldwide to gather data about the effects of specific AEDs on fetal and embryo development. These include (from largest to smallest) the European (or International) Registry of Antiepileptic Drugs and Pregnancy (EURAP), the UK Epilepsy and Pregnancy Register, the North American Antiepileptic Drug Pregnancy Registry, and the Australian Pregnancy Registry of Women on Antiepileptic Drugs.[27] The International Lamotrigine Pregnancy Registry has also been formed to monitor pregnancy outcomes in women who have been specifically exposed to that agent. A goal of the registries is to compare the risk for MCMs after maternal intake of different AEDs. Because the rate of MCMs is relatively low, the use of registries to create larger databases aids in detection of differences between specific drugs or treatment approaches (e.g., monotherapy vs polytherapy and dosing effects).

Three relatively consistent findings have been revealed by large registries as well as a number of smaller studies. AEDs increase the risk for MCMs, MCMs are more common with AED polytherapy than with monotherapy, and risk appears to be greater with valproate monotherapy than with other AED monotherapies. As of September 2006, more than 3,500 WWE had been entered in the UK Epilepsy and Pregnancy Register, and the overall rate of MCMs was 4.2% for women receiving an AED during pregnancy compared with 3.5% in untreated WWE.[28] Moreover, the frequency of MCMs was significantly higher with polytherapy than monotherapy (6.0% vs 3.7%, respectively), and for monotherapies the MCM rate was highest with valproate (6.2%). Earlier studies pointed to a dose-effect for valproate and the incidence of MCMs, particularly neural tube defects.[29]

Data from the North American Antiepileptic Drug Pregnancy Registry and the Australian Pregnancy Registry of Women on Antiepileptic Drugs also point to a significantly higher incidence of MCMs with valproate than with other AED monotherapies, particularly with doses above 1,100 mg per day.[30,31] Various other studies also have reported higher rates of MCMs with AED polytherapy than with monotherapy.[32–36] In a large nationwide, population-based register study in Sweden, the odds ratio for an MCM was 1.61 for infants exposed to AED monotherapy and 4.20 for infants exposed to AED polytherapy ($z = 3.0$; $p < 0.01$).[32] A French prospective cohort study reported that phenytoin plus phenobarbital was more teratogenic than phenobarbital alone,[35] and a collaborative group study in Japan reported progressive increases in the MCM rate as the number of AEDs increased from 0 to 4.[36] Data from the North American Antiepileptic Drug Pregnancy Registry also point to a high rate of MCMs with phenobarbital monotherapy (6.5% vs a background rate of 1.6%).[37]

The safety and the teratogenicity of many of the more recently introduced AEDs in pregnancy have not been thoroughly studied in humans.[38] The database is largest for lamotrigine through the International Lamotrigine Pregnancy Registry. Recent data from this registry point to an MCM rate of 2.9% with lamotrigine monotherapy, compared with generally reported rates of 2% to 3% in the general population and 3% to 5% in WWE exposed to AED monotherapy.[39] The MCM rate increased to 12.5% for lamotrigine plus valproate but was lower for other lamotrigine polytherapeutic regimens (2.7%). A prospective study from the UK Epilepsy and Pregnancy Register showed that lamotrigine doses were significantly higher for patients with an MCM than in those free of MCMs (352 mg vs 251 mg; $p = 0.005$).[40] The MCM rate was 5.4% in women receiving LTG doses of 200 mg/day and less than 2% in women receiving LTG doses of 200 mg/day or less. Table 2[38,41] presents a general overview of MCM rates in the general population and in WWE and various AED exposures based on reports in the literature.

In summary, a physician treating a pregnant woman with epilepsy must weigh the benefits of AED treatment with the risk for harm to the fetus. Current guidelines for the treatment of epilepsy in pregnant women recognize that children of women taking multiple AEDs appear to be at

Table 2 Reports of MCM rates by specific in utero exposures from various pregnancy registries and meta-analyses[38,40,41]

Type of in utero exposure	MCM rates (%)	OR or RR (95% CI) for MCMs
No AED, general population	1.6–3.2	
No AED, women with epilepsy	0.8–3.1	OR 0.99 (0.92–4.00)
All AED exposures	3.1–9.0	OR 1.86 (1.42–2.44); RR 2.2–2.5 (1.2–5.0); OR 3.26 (2.15–4.93)
Polytherapy	6.5–18.8	OR 5.1 (1.0–21.1)
Monotherapy	2.3*–7.8	OR 2.6 (0.8–8.3)
Phenobarbital	4.7–6.5	OR 2.7 (0.6–16.4); RR, 4.2 (1.5–9.4)
Phenytoin	0.7–9.1	OR, 1.64 (0.48–5.62); OR 1.9 (0.3–9.2)
Primidone	14.3	OR 5.3
Carbamazepine	2.3–5.7	OR 2.21 (1.44–3.39); RR 2.24 (1.1–4.6); OR 2.5 (1.0–6.0); OR 3.0 (0.6–16.0); RR 4.9 (1.3–18.0)
Valproate	5.9–16.0	OR 2.78 (1.62–4.76); OR 4.1 (1.5–11.0); RR 4.9 (1.6–15.0); OR 4.0; RR 5.0 (2.9–8.6); OR 2.51 (1.43–4.68 compared with carbamazepine)
Lamotrigine	2.0–3.2	OR 1.44 (0.77–2.67)
Gabapentin	3.2	OR 1.33 (0.17–10.20)
Topiramate	7.1	OR 2.75 (0.62–12.20)
Oxcarbazepine	2.4	

MCM = major congenital malformation; OR = odds ratio; RR = relative risk; CI = confidence interval; AED = antiepileptic drug.
*For AED monotherapies other than valproate.

higher risk for malformations and developmental delays.[5] The guidelines recommend AED monotherapy at the lowest possible dose during pregnancy. Although valproate may not be the best choice of therapy for many women desiring to become pregnant, drug choice should ultimately be based on seizure type, with strong consideration for the agent that will provide optimal seizure control with the fewest side effects.[1,5,9]

In addition to optimizing pharmacotherapy before pregnancy, a number of steps can be taken to minimize the risk for MCMs posed by AED exposure in utero. For example, counseling before pregnancy should include discussion of preconceptional and gestational folate supplementation as prevention against malformations of the neural tube.[12] Some AEDs can interfere with the absorption and metabolism of folate, which is required to support normal fetal development. Before defects in neural tube closure occur before a woman is likely to know that she is pregnant, folic acid supplementation in WWE is recommended for 3 months before pregnancy and throughout the first trimester.[1,12] The optimal folate dose for prevention of neural tube defects is not completely clear, but many physicians recommend a daily dose in the range of 1 to 4 mg/day.[42]

Infants exposed to hepatic CYP450 enzyme-inducing AEDs in utero are at risk for vitamin K deficiency that can result in coagulopathy and neonatal intraparenchymal and intracerebral hemorrhage during the first 24 hours of life.[5,9,12] It is therefore recommended that pregnant WWE taking AEDs should receive vitamin K 10 mg/day by mouth during the last month of pregnancy.[5,9,12] If the mother has not received vitamin K during the last month of pregnancy, it should be administered as soon as possible after the onset of labor.[5] In addition, the neonate should receive vitamin K 1 mg IM at birth.[5,12]

There are no contraindications to breastfeeding for WWE. In general, the benefits of breastfeeding for both infant and mother are believed to outweigh the small risk for adverse events associated with AEDs.[5] Although concentrations of AEDs in breast milk are generally low and are not harmful to the infant, clinical observation of infants for adverse effects such as sedation and poor feeding, specifically seen with exposure to barbiturates and benzodiazepines,[9,12] is warranted.

SEIZURES, AEDS, AND POSTMENOPAUSAL WOMEN Peri- and postmenopausal WWE present special challenges for seizure management, including possible changes in seizure patterns related to changing hormone levels or use of hormone replacement therapy, as well as heightened concerns about risks for osteoporosis related to AED treatment.

That reproductive hormones may affect seizure propensity is suggested by the phenomenon

of catamenial epilepsy, i.e., changes in seizure frequency related to the menstrual cycle. In addition, studies have shown that risk for seizures increases during perimenarche in girls with preexisting epilepsy.[43] Changes in hormone patterns during the early or perimenopausal period can lead to an increase in the estrogen:progesterone ratio that translates into an increased occurrence of seizures.[44,45] However, only a subset of patients appear to experience such an increase, particularly those with a history of catamenial epilepsy. After menopause, reproductive hormone levels are more stable than during the reproductive years and the perimenopausal period and may be associated with a decreased propensity for seizures, especially for those with a history of catamenial epilepsy. On the other hand, use of hormone replacement therapy has been associated with a dose-related increase in seizure frequency in postmenopausal WWE.[46]

The other major concern in postmenopausal WWE is the risk for bone fracture due to the effects of many AEDs on bone density. In particular, use of enzyme-inducing AEDs may interfere with calcium absorption and vitamin D metabolism, resulting in decreased bone mineral density and accelerated osteoporosis.[45] It is recommended that all WWE receive adequate calcium and vitamin D supplementation and engage in weight-bearing exercise.[47] This is important for all women but becomes an even greater concern in postmenopausal women.

CONCLUSIONS Women with epilepsy present unique challenges for medical professionals involved in their care. Of particular concern is the management of seizures in women of childbearing age because of the potential risks posed by seizures, and especially by AEDs, to the developing embryo or fetus. Current guidelines for seizure management during pregnancy recommend AED monotherapy at the lowest possible dose during pregnancy, noting that drug choice should ultimately be based on seizure type, with strong consideration for the agent that will provide optimal seizure control with the fewest side effects. These recommendations are based on the recognition that the risks for MCMs are significantly greater with AED polytherapy than with monotherapy and on the identification of dose-related teratogenic risk with at least some AEDs. Monotherapy may also improve compliance and reduce drug costs.

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