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2005 AES Annual Course: Evidence Used to Treat Women with Epilepsy

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Summary: Although most female-specific considerations for treatment of epilepsy cannot be answered by Class I evidence, significant progress in our knowledge base has occurred in the past few years. Open-label studies of progesterone supplementation showed promising results; an ongoing randomized trial may provide definitive evidence for therapeutic use of progesterone in women. A randomized trial of hormone replacement therapy demonstrated a dose-related increase in seizure frequency in postmenopausal women with epilepsy. The use of different AED regimens during pregnancy cannot be explored with randomized, controlled trials; we must rely on the best available evidence from ongoing observational studies. The consistent findings of large prospective pregnancy registries reveal a consistent pattern of amplified risk for major congenital malformations in pregnancies exposed to valproate. These registries have also highlighted the concern for the effect of shifting hormones on AED concentrations. An increased frequency of seizures during pregnancy has been noted with lamotrigine (LTG) and oxcarabazepine, both of which undergo glucuronidation. Other studies have demonstrated an increased clearance of LTG during pregnancy and with exogenous estrogen use. It may be prudent to closely monitor serum concentrations of these AEDs with hormonal changes. An increased risk for neurodevelopmental consequences has been demonstrated for the fetus exposed to AED polytherapy, valproic acid, or frequent maternal convulsive seizures. Preliminary information about breastfeeding with LTG and levetiracetam is available. These newly released findings provide the tools to begin to practice evidence-based medicine when treating our female patients during their reproductive and postmenopausal years. **Key Words:** Epilepsy—Women—Hormones—Pregnancy—Antiepileptic drugs—Breastmilk—Menopause—Malformations.

Initial presentation of a patient to the physician is laden with medical decisions and dilemmas. What are the most relevant symptoms and signs? What is the differential diagnosis in order of likelihood, but also prioritizing urgency? What diagnostic tests should be performed? And what are the best treatment options? Although overall epilepsy incidence does not discriminate based on gender, it is the dilemma of which treatment option is best that must be approached with a special armamentarium of tools when selecting antiepileptic drugs (AEDs) for girls, teens, and women. In addition to the usual considerations of efficacy for seizure type, tolerability, and idiosyncratic side effects, the prescribing physician should also consider the following issues. What are the adverse effects of AEDs on bone, metabolic, and reproductive health? What is the relationship between seizures and hormones? Can seizures be worsened by exogenous hormone administration? Do the effects of hormones on seizures offer us any helpful treatment options? What about birth control? Can hormonal contraceptives affect seizures? AED concentrations? What will happen with the menopausal transition and its treatment? Can a woman on AEDs have a safe pregnancy? What are the risks to the developing fetus? What are the immediate risks (fetal death, major congenital malformations (MCM)) versus long-term risks (neurodevelopment)? Can risks be modified by treatment selection? Will seizures worsen during pregnancy? What extra precautions should occur during pregnancy? If on an AED during pregnancy, which AED is safest to the developing fetus? What evidence is there to differentiate safety risks for the AEDs? When should folate begin? How much? What is the evidence that folate is protective for women on AEDs? Can the patient breastfeed on AEDs? Which ones?

Physicians are encouraged, if not mandated by guidelines, insurance companies, and the legal system, to select treatment options according to evidence based medicine. However, most of these gender-specific considerations for

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females with epilepsy cannot be answered by Class I evidence (prospective, randomized, controlled clinical trials with masked outcome assessment in a representative population). Nonetheless, we have made advancements in our knowledge base in the past few years in several of these areas. The summary that follows is not a comprehensive review of all available data on female-specific issues, but instead highlights recent reports from key clinical studies and provides a glimpse of current, ongoing clinical research trials.

EFFECTS OF SEX STEROID HORMONES ON EPILEPSY IN WOMEN

Catamenial epilepsy is the term applied when the pattern of seizure occurrence in a woman fluctuates with the menstrual cycle. In studies of women with intractable localization-related epilepsy, 33–39% of women demonstrated a catamenial pattern (1,2). This fluctuation has been attributed to the neuroactive properties of sex steroid hormones and the cyclic variation of their serum levels. The effects of 17beta-estradiol (estradiol) and progesterone in animal studies are compelling. Estradiol increases seizure activity, while progesterone has anticonvulsant properties. Many cellular and molecular mechanisms contribute to the changes in brain excitability mediated by these hormones. Much of the antiseizure effect of progesterone may be due to the conversion to the metabolite allopregnanolone (5alpha-pregnan-3alpha-ol-20-one), a $GABA_A$-receptor–modulating neurosteroid (3).

An understanding of the effects of hormones on seizure susceptibility may provide an opportunity to use hormones as therapy in women with intractable epilepsy. Open-label studies of progesterone supplementation have shown promising results (4,5). Herzog et al., is currently conducting a multicenter, double-blind, randomized, placebo-controlled trial of cyclic progesterone lozenges in the treatment of women with localization-related epilepsy (2). The study includes both catamenial and noncatamenial groups. If benefits of progesterone supplementation are demonstrated, subgroup analysis will identify whether the benefits can be extended to all women with epilepsy or are limited to those who appear more susceptible to the cyclic variations in estradiol and progesterone with a catamenial pattern. If this study is positive, physicians will not only be able to acknowledge the effect of cycling hormones on seizures, but be able to use this relationship to their advantage in selecting treatment options.

MENOPAUSE AND ITS TREATMENT

Perimenopause is marked by erratic and frequently high estrogen levels, while postmenopause is characterized by stable, low estrogen levels (6). Although preliminary, a retrospective questionnaire study suggested that seizure frequency can increase with perimenopause and can improve once the menopausal transition is complete (7). This alteration in seizure pattern was more likely to occur in women who experienced a catamenial pattern during their reproductive years. In the postmenopausal group, hormone replacement therapy (HRT) was significantly associated with an increase in seizures.

Acknowledging the limitations of a retrospective study based on a patient questionnaires, Harden et al., initiated a multicenter, double-blind, randomized, placebo-controlled trial of the effects of two doses of Prempro (CEE/MPA) (0.625 mg of conjugated equine estrogens, plus medroxyprogesterone acetate, 2.5 mg) on seizure control (8). Subjects received either placebo, single-dose CEE/MPA, or double dose CEE/MPA. Twenty-one subjects were randomized after completing baseline. Five out of seven subjects (71%) on double-dose CEE/MPA had a worsening seizure frequency of at least one seizure type, compared to 4/8 (50%) on single dose CEE/MPA and 1/6 (17%) on placebo ($p = 0.05$). Increasing CEE/MPA dose was also associated with an increase in the frequency of the subject's most severe seizure type ($p = 0.008$) and of complex partial seizures ($p = 0.05$). Despite the limited enrollment of this study, the conclusion could still be made that CEE/MPA was associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy (8).

This study in postmenopausal women with epilepsy was halted early due to findings from the Women's Health Initiative (WHI) study: overall health risks after 5 years of follow-up clearly exceeded benefits from use of single dose CEE/MPA in healthy postmenopausal U.S. women (9). Although the released findings from the WHI study has resulted in decreased long-term HRT use for preventive health measures, HRT is still frequently used as treatment for perimenopausal symptom relief. The findings from Harden et al. (8) raise caution even for the short-term use of CEE/MPA in women with epilepsy. However, synthetic progestins such as medroxyprogesterone acetate are not metabolized to the active neurosteroid allopregnanolone. Future studies of whether an estrogen with natural progesterone could circumvent the risk for increased seizures would be beneficial for women with epilepsy.

BENEFITS OF FOLIC ACID SUPPLEMENTATION

One treatment paradigm that is generally accepted as important is the use of supplemental folic acid prior to conception and during pregnancy in women on AEDs (10). However, the established benefits of supplemental folic acid are based on studies of women without epilepsy in the general population (11) or women at high risk for neural tube defects, with a positive family history (12). Studies specifically designed to determine the effects of fetal AED exposure have failed to show a protective effect

against major malformations with folic acid administration (13–15). These findings either could be due to folic acid's inability to impact AED teratogenic mechanisms or, possibly, to the prescription of inadequate dosage levels of folic acid.

USE OF AEDS DURING PREGNANCY

Epilepsy is the most common neurologic disorder that requires continuous treatment during pregnancy, and AEDs are one of the most frequently administered chronic teratogen exposures (16,17). The fetal anticonvulsant syndrome consists of various combinations of the following features: MCM, minor anomalies, intrauterine growth retardation, cognitive dysfunction, microcephaly, and infant mortality. Several previous studies have demonstrated that the risk for developing features of the fetal anticonvulsant syndrome is higher with AED polytherapy than monotherapy regimens (18). Previous guidelines recommended the use of monotherapy during pregnancy with the AED that best controlled that individual's seizure types (10). However, data recently released from several ongoing pregnancy registries illuminate that there are significant, differential risks for MCM among the various AED monotherapy regimens.

Use of different AED regimens during pregnancy cannot be explored with randomized, controlled trials (Class I evidence), and most existing reports do not even meet Class II evidence criteria. Thus, prescribing physicians are forced to consider the best available evidence from ongoing observational studies in making treatment decisions. Several limitations are common to all pregnancy registries. Inclusion of only true prospective cases with enrollment before the first structural ultrasound is important to prevent a biased sample. Individual AED monotherapies need to be considered as pure groups and separate from any polytherapy combinations. Power calculations can be intimidating. For example, with an overall major malformation rate of 2% in the general population, the number of cases needed on a particular AED to detect a relative risk of two with 80% power will be 555. Even more daunting, a teratogenic drug will not increase all major malformations, but more often will increase the risk for a particular major malformation. To detect an increase in specific malformations which have an incidence of 1/1,000 such as cleft lip/palate or spina bifida, it would take 3,655 patients to detect a 3-fold relative risk.

Worldwide, there are several large-scale AED pregnancy registries that are prospective studies of anatomical defects and major adverse outcomes. The most notable ones include EURAP, the North American Pregnancy Registry, the UK Epilepsy and Pregnancy Register, and the Australian Pregnancy Registry. Several pharmaceutical companies also keep internal pregnancy registries. The largest prospective study is through GlaxoSmithKline for outcomes of lamotrigine (LTG) exposures. Although there are many design differences among the pregnancy registries, all are observational prospective studies. The registries differ in how major malformations are defined, up to what age identification of major malformations may be included (birth to 1 year), and whether findings of spontaneous, elective, or therapeutic abortions are included. Because of these design differences, pooling data from different pregnancy registries would not be scientifically valid. Most of the women enrolled in these pregnancy registries were on monotherapy regimens with good seizure control. The most commonly prescribed AEDs across the pregnancy registries are carbamazepine (CBZ), valproate (VPA), and LTG. Most of the findings are reported as percentage of total infants exposed to a certain medication in utero who have a major malformation, with 95% confidence intervals (CI). CI are particularly valuable when examining observational association and causation studies.

EURAP (19) is a prospective registry in 39 countries and has enrolled 7,236 mothers with 4,134 completed outcomes. Although specific AED MCM outcomes are not available yet, this promises to be a wealth of information in the next few years. The North American AED Pregnancy Registry has enrolled 4,376 women with 76% on monotherapy, and 67% pure prospective cases, and has had two major outcome reports. The North American AED Pregnancy Registry uses only prospective enrollees, identifies major malformations up to 5 days of life, and adheres to relatively rigid criteria for release of findings with approval by a scientific advisory committee. Results have been released for only two medications thus far, phenobarbital (PB) and VPA. Of 77 women receiving PB monotherapy, five of the infants had confirmed major malformations (6.5%; 95% CI 2.1–14.5%). When compared to the background rate for major malformations in this hospital-based pregnancy registry (1.62%), the relative risk was 4.2 (95% CI 1.5–9.40) (20).

Findings of VPA monotherapy exposure from the North American AED Pregnancy Registry were released last year (21). Of the 149 infants with in utero VPA exposure, 16 (10.7% (95% CI 6.3–16.9)) had MCM. Malformations included spina bifida, heart defects, urogenital defects, and multiple anomalies. The relative risk compared to the external comparison group was 7.3 (95% CI 4.4–12.2). Perhaps more relevant to the prescribing physician is the relative risk compared to the internal comparison group. The internal comparison group was the major congenital malformation rate (2.9%) of three other AED monotherapy regimens; the relative risk of VPA for malformations compared to this group was 4.0 (95% CI 2.1–7.4).

The current release criteria the North American AED Pregnancy Registry established for no associated increase in the frequency of all major malformations is particularly hard to demonstrate; it is met when the upper end of the

95% confidence limit does not exceed 2.0. compared to the external comparison group (22). Because of the difficulty in obtaining these strict criteria and the number of pregnancy exposure it would require, the recent proposal is that the North American AED Pregnancy Registry may release information for all monotherapy regimens in 2007 and polytherapy regimens in 2008.

The UK Epilepsy and Pregnancy Register has collected prospective, full outcome data on 3,607 cases (23). MCM detected within the first 3 months of life were included. The overall MCM rate for all AED exposures was 4.2% (95% CI 3.6–5.0%). The MCM rate was higher for polytherapy than monotherapy (6.0 vs. 3.7%; adjusted OR 1.83). Polytherapy combinations containing VPA carried a higher risk of MCM than combinations not containing VPA (OR = 2.49 (95% CI 1.31–4.70)). The MCM rate for the monotherapy group did not differ substantially from the group of women with epilepsy on no AEDs during pregnancy, 3.5% (95% CI 1.8–6.8%). Comparisons between monotherapy regimens did reveal a statistically significant increased MCM rate for pregnancies exposed to VPA (6.2% (95% CI 4.6–8.2%)) compared to those exposed to CBZ (2.2% (1.4–3.4%) (adjusted OR = 2.97 ($p < 0.001$)). Although a lower MCM rate was identified for pregnancies exposed to LTG (3.2% (95% CI 2.1–4.9), the adjusted OR 0.59 compared to the VPA group was not statistically significant ($p = 0.064$). A positive dose response for MCMs was found for LTG ($p = 0.006$), with reports of a MCM rate for doses >200 mg/day of 5.4% (95% CI 3.3–8.7). The dose trend for VPA was not statistically significant (9.1% for doses >1,000 mg/day vs. 5.1% for doses ≤1,000 mg/day) (23).

The finding from the UK Pregnancy Register that the CBZ monotherapy group had the lowest MCM rate is not a new finding, but it is often overlooked. It highlights the importance of not assigning all old AEDs to one category versus new AEDs with regard to risk during pregnancy. The newer generation of AEDs consists of a large number of structurally diverse compounds, most of which have demonstrated teratogenic effects in preclinical animal experiments. With the exception of LTG, none of the agents have been sufficiently tested during human pregnancy to assess their safety or teratogenicity. Prospective population-based studies in postmarketing evaluation with larger numbers of patients are essential to establish safety in human pregnancies.

The International LTG Pregnancy Registry began in 1992 and is supported by GlaxoSmithKline (24). Outcomes of 1,246 pregnancies are available. Of the 707 outcomes from 1st trimester exposure to LTG monotherapy, 20 malformations have been detected, for a MCM rate of 2.8% (95% CI 1.8–4.4). Risk for MCM with LTG polytherapy differed according to whether the combination included VPA. Polytherapy exposures with LTG that did not include VPA demonstrated a MCM rate of 2.7% (95% CI 1.0–6.6). Polytherapy exposures with VPA demonstrated a MCM rate of 11.7% (95% CI 6.6–19.5). The database has been reexamined in light of the findings of the UK Pregnancy Register of a dose effect. The mean dose in the group with defects was 250.7 mg/day, and the mean dose in the group without defects was 281.1 mg/day. Median doses for both groups were 200 mg/day. Other studies will help to determine if the dose response effect is replicated.

Early outcome data was released from the multicenter, observational study Neurodevelopmental Effect of AEDs (NEAD) (25). This ongoing prospective study spans 25 epilepsy centers in the United States and United Kingdom. The primary aim of the study is to determine if long-term neurocognitive outcomes are different among four different monotherapy exposures in utero (LTG, CBZ, VPA, and phenytoin (PHT)). Early outcomes in this cohort of 333 mother/child pairs have been released recently. Serious adverse outcomes were defined as fetal death and/or MCM. Frequencies of pregnancies resulting in serious adverse outcomes for each AED differed significantly and were: LTG 1.0%, CBZ 8.2%, PHT 10.7%, and VPA 20.3%. These differences were not explained by other factors and a dose dependent effect was observed for VPA. Further analysis of the individual adverse outcomes revealed that MCM were more common for VPA ($p \leq 0.0003$). The relative risks (95% confidence limits) of MCM for VPA relative to each AED were: VPA versus LTG 22.82 (4.25–424.20). VPA versus CBZ 4.59 (1.58–15.34), and VPA versus PHT 2.87 (0.91–11.02) (25).

The Australian Pregnancy Registry has enrolled over 800 women (26,27). Significantly greater risk for MCM on VPA monotherapy was demonstrated (17.1%) compared to other AED monotherapy exposures (2.4%) and no AED exposures (2.5%). The MCM rate increased with increasing VPA dosage ($p < 0.05$) with a MCM rate of >30% for doses >1,100 mg/day. Other MCM rates reported were PHT 4.7%, CBZ 4.5%, and LTG 5.6% for monotherapy exposures.

The consistent findings of these large prospective pregnancy registries scattered across different regions of the world reveal a consistent pattern of amplified risk for the development of MCM in pregnancies exposed to VPA.

EFFECT OF SHIFTING HORMONES ON AED CONCENTRATIONS

One concern raised by the prospective data set from the Australian Pregnancy Registry was the observation that an increased frequency of seizures occurred in the second and third trimesters for the LTG group compared to the VPA and CBZ groups (28).

Serum concentrations of all AEDs are reduced during pregnancy; however, the magnitude of alterations in LTG concentrations exceeds that described for the older AEDs,

which are primarily eliminated via the cytochrome P450 system (29). Approximately 90% of LTG undergoes hepatic glucuronidation, catalyzed by UGT1A4, an isozyme of the UGT family of enzymes. This elimination pathway appears particularly susceptible to activation during pregnancy, possibly as a result of direct effects of rising sex steroid hormone levels. A study of 14 pregnancies on LTG monotherapy demonstrated that clearance significantly differed between preconception baseline and each trimester and between trimesters. LTG clearance progressively increased until 32 weeks' gestational age, reaching a peak of >330% of baseline (30). LTG clearance rapidly decreases to baseline in the first two weeks postpartum. Two small studies have illuminated the potential clinical impact of gestation-induced changes in LTG metabolism. Twelve pregnancies in 9 women were followed on LTG monotherapy. Nine of the 12 pregnancies exhibited seizure worsening, most commonly 12–28 weeks gestational age. After delivery, toxic side effects were noted in some women with the rapid return to baseline of LTG metabolism. Another retrospective study of 11 pregnancies on LTG monotherapy noted seizure worsening in five pregnancies (31). A significant decrease in the ratio of LTG concentration-to-dose by 65% was observed during the second and third trimesters, compared to preconception baselines. All women that had a greater than 60% change in level/dose ratio had seizure worsening, which was most likely to occur in the expected time frame from prior studies, 18–35 weeks of gestation. All three studies noted substantial inter-patient variability in the pharmacokinetic changes during pregnancy, and recommended close monitoring of LTG concentrations throughout the entire pregnancy with appropriate dosage adjustments to minimize the potential of seizure worsening (31–33).

The effect of sex steroid hormones on LTG metabolism is not unique to pregnancy. Several recent studies have demonstrated increased clearance in LTG in women on hormonal contraceptives. In a study of 22 women on LTG in combination with oral contraceptives (OC) and 30 women on LTG without OC, the LTG plasma levels relative to dose and body weight were significantly reduced by >50% with coadministration of OC (34). A more recent prospective study separated the contraceptive group according to whether the women were on ethinyl estradiol (EE)-containing preparations or progesterone-only containing compounds (35). LTG serum concentration-to-dose ratio (CDR) was significantly lower in women using EE than in the control group; the CDR of the progesterone group was not different from controls. Of the women who switched from the control to the EE group, considerable reductions in their CDRs occurred, and an increase in CDR occurred in the two women who changed from EE to progesterone-containing compounds. It appears that it is the estrogen component of contraceptive preparations that induces the increase in LTG metabolism. The study of HRT in postmenopausal women with epilepsy also noted that subjects randomized to receive HRT had a decrease in LTG levels of 25–30% while taking CEE/MPA (8). These finding should be considered when treating women during their reproductive and postmenopausal years. Initiation or discontinuation of estradiol-containing compounds may necessitate LTG serum concentration monitoring and dosage adjustment. Although none of these studies were able to determine if the alterations in LTG pharmacokinetics were clinically relevant with regard to seizure control or toxic side-effects, it is unlikely that a controlled, randomized study would be performed to demonstrate seizure worsening with lowering of LTG serum concentrations by coadministration of exogenous ethinyl estradiol.

The discovery that glucuronidation can be activated by hormonal shifts may apply to other AEDs. Metabolism of VPA is 30–50% by glucuronidation, and 50–60% of the clearance of oxcarbazepine (OXC) is via glucuronidation. Related observations on seizure control and treatment were just released from the international EURAP Epilepsy Pregnancy Registry (36). Data was obtained from 1956 pregnancies in 1,882 women with epilepsy. The majority of women (58.3%) were seizure-free throughout pregnancy. Seizure frequency remained unchanged throughout pregnancy in 63.6%, was increased in 17.3%, and decreased in 15.9%. Factors that were associated with an increased risk for occurrence of all seizures were localization-related epilepsy (OR: 2.5; 1.7–3.9) and polytherapy (OR: 9.0; 5.6–14.8). OXC monotherapy was associated with a greater risk for occurrence of convulsive seizures (OR: 5.4; 1.6–17.1). The number or dosage of AEDs were more often increased in pregnancies with seizures (OR: 3.6; 2.8–4.7) or pregnancies treated with OXC monotherapy (OR: 3.7; 1.1–12.9) or LTG monotherapy (OR: 3.8; 2.1–6.9). This international, observational study did not dictate a protocol to monitor serum levels or make dosage adjustments (36). The apparently higher risk of convulsive seizures among women treated with OXC and the need to increase dose or other meds with OXC or LTG monotherapy is consistent with similar major routes of elimination via glucuronidation and requires further pharmacokinetic studies. It may be prudent to closely monitor OXC as well as LTG serum concentrations during pregnancy.

DIFFERENTIAL RISKS OF AEDS ON NEURODEVELOPMENT OF THE OFFSPRING

The majority of studies investigating cognitive outcomes in children of women with epilepsy report an increased risk of mental deficiency, affecting 1.4–6% of these children compared to 1% of controls (37). A variety of factors contribute to the cognitive problems of children of mothers with epilepsy, but recent information

from studies highlight that risks may differ substantially between different AEDs. The large-scale pregnancy registries represented throughout the world are particularly limited in the ability to detect adverse neurocognitive effects from in utero exposure to different AED regimens. The cohort would ideally be followed with rigorous, standardized neuropsychometric testing over several years. One large, multicenter study including sites across the United States and in the UK is the Neurodevelopmental Effects of AEDs (NEAD) by Meador et al. (25). This study intends to follow all offspring with detailed neuropsychometric batteries until age 6 years old to detect any differences between children exposed in utero to four different monotherapy regimens: PHT, VPA, CBZ, and lamotrigrine.

A retrospective survey in the UK suggested an especially high risk of VPA for the neurodevelopment of children exposed in utero (38). Compared to children of women with epilepsy on no AEDs, the odds ratios for additional educational needs were 1.49 for all children exposed to AEDs in utero and 3.4 for children exposed to VPA monotherapy. A prospective study conducted in Finland tested 182 preschool or school age children that had prenatal exposure to AEDs and compared them to 141 control children. Eighty-six children were exposed to CBZ monotherapy and 13 to VPA. Significantly reduced verbal IQ scores were found in the polytherapy group and in the VPA monotherapy group, although the latter group was confounded by low maternal education (39). In this study the CBZ group actually demonstrated no differences from controls in their mean verbal and nonverbal IQ scores. A follow-up study from the UK group performed a battery of neuropsychological tests on mother-child pairs on 249 children ages 6–16 years old. Children with in utero exposure to VPA had a significant reduction in verbal IQ (10–14 points) when compared to children exposed to other AED monotherapies or the general population (40,41). Other significant predictors of verbal IQ were the mother's IQ, and the number of convulsive seizures (41). Greater than five convulsive seizures during pregnancy had a negative effect on verbal IQ (40).

The findings of increased risk for neurodevelopmental consequences with polytherapy, VPA exposure, and with frequent convulsive seizures should be considered by the prescribing physician and included in the discussion with women with epilepsy.

BREAST-FEEDING ON AEDS

The benefits of breast-feeding are numerous and include reduced infant mortality, fewer infectious diseases, decreased risk of immunologically mediated disorders, such as type 1 diabetes mellitus, and possibly even enhanced cognitive development (42). Current recommendations are that, in the absence of contraindications, women should breast-feed their infants for at least the first 12 months of life (43). Any decision to limit breast-feeding must be justified by the fact that the risk to the baby clearly outweighs the benefits of nursing. Unfortunately, this practical directive will never be supported by data obtained through randomized, controlled trials. What is the risk to babies who nurse while their mother is taking medication, and what is the specific risk among different AEDs? Anticipated risks include rash, hepatic dysfunction, hematologic disorders, and immediate CNS side-effects, such as lethargy, poor suck, and reduced feeding, with slow growth; in addition, long-term neurocognitive development may be effected. The American Academy of Neurology supports breast-feeding for infants of women on AEDs (44), but pediatricians often require further detailed information on the amount of AED excreted into the breast milk. Current recommendations regarding infant safety are to use caution with administering PB, ethosuximide, and primidone to lactating women, as levels of exposure to infants respectively are estimated at 100%, 50%, and $>10\%$ of the weight-adjusted therapeutic dose (42). In contrast, the estimated levels of exposure for CBZ, PHT, and valproic acid are 3–5% of the therapeutic dose, standardized by weight, and are considered acceptable medications for women who are breastfeeding (42,43).

Recent studies of nursing child-mother pairs with LTG estimate that infant exposure through breast milk is approximately 10% of the therapeutic dose. Modest infant serum LTG levels were reported, and the infants had no adverse outcomes (42,45,46). A recent study of levetiracetam reported breast milk concentrations within the recommended safe exposure index of $\leq 10\%$ with low infant serum concentrations and no adverse effects (47). These studies provide important preliminary information regarding safety of breast-feeding on LTG and levetiracetam and may offer women the option of giving their infants the medical and psychosocial benefits of breast-feeding.

CONCLUSIONS

The consistent findings of increased risk for MCM and neurodevelopmental delay with VPA use during pregnancy should enter into the physician's daily treatment decisions. Given that 50% of pregnancies are unplanned in the United States, prescribing AEDs to females during their reproductive years should be performed with the constant consideration of pregnancy, planned or unplanned. AED monotherapy is the goal, possibly at the lowest effective dose for seizure control. With the now recurring signals of concern for VPA, other medication trials in an individual patient are not only strongly recommended but necessary to decrease the risk of adverse fetal consequences. For women who fail other AEDs and require VPA, the dose should be limited if possible.

Fetal outcomes can be improved further with clarification of discriminating risks among other AED regimens. Additional information on newer generation AEDs should be forthcoming in the next five years. Valuable information will not only include fetal outcomes, but information regarding pharmacokinetic alterations during pregnancy and how to monitor and adjust individual AEDs to maintain maternal and fetal health. In the absence of Class I evidence, clinicians must select AEDs using information that is currently available from observational studies, with constant reassessment as new findings are reported.

An improved understanding of the effects of sex steroid hormones on epilepsy in women and the effects of shifting hormones on AED concentrations will allow us to better care for females with epilepsy during different life stages. The current randomized progesterone trial may provide Class I evidence for therapeutic use of hormones to improve seizure control for women.

Despite the practical and ethical limitations of study design for many of the treatment considerations for women with epilepsy, recent studies have provided valuable and valid, scientific-based information. With the anticipation of release of additional findings from current, ongoing well-designed studies, we can begin to practice evidence-based medicine when treating our female patients with epilepsy.

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