Special Article

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Practice parameter

Management issues for women with epilepsy (summary statement)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Overview. The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) develops practice parameters to assist neurologists in the management of specific patient populations. Management issues for women with epilepsy (WWE) who take antiepileptic drugs (AEDs) during their reproductive years are numerous and complex. The use of evidence-based parameters for these management points may lead to improved family planning, seizure management, pregnancy outcomes, and patient satisfaction for WWE. Questions that have guided the development of this practice parameter have been divided into those relevant for WWE during reproductive years and those addressing management issues for women during pregnancy and the postpartum period (table).

The development of this parameter was undertaken by members of the AAN QSS in conjunction with the American Epilepsy Society (AES), the Epilepsy Foundation of America (EFA), and the Child Neurology Society (CNS).

Justification. Epilepsy affects approximately 1% of the population. There are potentially over one million WWE of childbearing age in the United States. It has been estimated that 3 to 5 births per thousand will be to WWE.

Health issues for WWE are complex and multifaceted. The fertility rate of WWE is lower than that of women in the general population. In contrast, many AEDs interfere with the efficacy of hormonal contraception. All major AEDs in common use have been associated with congenital malformations. However, frequent or unremitting convulsive seizures may damage the fetus by producing reduced placental blood flow and impaired fetal oxygenation.

WWE constitute a group for whom principal care by a neurologist for epilepsy management may be indicated. They will benefit from both optimal AED management and the support and coordination of care that can be provided by a longitudinal doctor-patient relationship.

Description of process. An OVID MEDLINE literature search was conducted for the period 1965 to 1996 using the following key words/phrases and cross referencing: epilepsy/seizures and pregnancy, anticonvulsants, antiepileptic drugs, teratogenesis, oral contraceptives, birth defects, folate/folic acid, vitamin K, and breast-feeding. A total of 154 titles were provided. Reviews, letters, and case reports were excluded. Literature concerning hormonal fluctuation and seizure threshold, AED teratogenesis, and folate effects in animals was reviewed. Bibliographies from articles in published AAN Consensus Guidelines (1992) and review articles on topics pertaining to WWE were surveyed for additional references. Forty-six retrospective and prospective studies with and without controls were reviewed, 35 contributing Class II and 11 contributing Class III evidence. These included studies evaluating pregnancy outcomes in WWE, folate supplementation for WWE, and the use of vitamin K during pregnancy for WWE. No randomized, controlled trials contributing Class I evidence specifically referable to WWE were found. Class I evidence pertaining to the effi-

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See Appendix 2 on page 948 for a list of subcommittee members.

From the American Academy of Neurology.

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Address correspondence and reprint requests to AAN, 1080 Montreal Ave., St. Paul, MN 55116.

Table *Management issues for women with epilepsy*

During reproductive years
What is the best AED regimen during reproductive years?
What is the best contraceptive plan?
What is the role of folic acid supplementation during reproductive years?
How should seizures related to cyclic hormonal fluctuation be managed?
What are the appropriate topics for prepregnancy counseling?
During and after pregnancy
How should AED levels be monitored and adjusted during pregnancy?
What is the role of vitamin K use during pregnancy?
What recommendations can be made regarding breast-feeding?
How should AED dosages be altered in the postpartum period?

AED = antiepileptic drug.

cacy of folate supplementation for primary and secondary prevention of neural tube defects in the general population was reviewed.

Parameter drafts were circulated to selected experts in epilepsy and to the American College of Obstetrics and Gynecology (ACOG), American Academy of Pediatrics (AAP), and CNS.

Conclusions. *Reproductive years.* AED regimen. The AED most appropriate for seizure type and the drug producing optimal control with least side effects remains the AED of choice for WWE. Heredity, socioeconomic status, and other determinants of maternal health all play a role in the production of adverse pregnancy outcomes in WWE. Evaluation of these issues is epidemiologically difficult, and contradictory reports appear in the literature. Strong scientific evidence is available regarding the teratogenic effects of AEDs in animals. Information available from human studies is less clear but implicates AEDs as human teratogens. A specific syndrome referable to one drug is less likely than previously suggested, although there is evidence that the risk for neural tube defects may be greatest for infants of WWE taking valproic acid/divalproex sodium (1%) and carbamazepine (0.5%). Children of women taking multiple AEDs appear to be at higher risk for congenital malformations and developmental delay. The teratogenic potential for the newer AEDs—felbamate, gabapentin, lamotrigine, tiagabine, topiramate, and vigabatrin—is unknown at this time.

If WWE have been free of seizures on an AED for a period of time, discussion regarding medication withdrawal should be undertaken. The AAN QSS recommends as a guideline that discontinuation of AEDs may be considered in a patient who has been seizure free for 2 to 5 years and has a single type of seizure, normal neurologic examination/IQ, and an EEG that has normalized with treatment. For WWE during their reproductive years, the teratogenic risks of AEDs and their potential to interfere with the efficacy of hormonal contraception are factors that must be considered in the decision to attempt AED withdrawal. WWE who are contemplating pregnancy or the use of hormonal contraception may wish, after appropriate counseling, to assume the potentially greater risk of seizure occurrence even if the above criteria have not been met. Risk for seizure recurrence is cumulative but greatest in the first 6 months after discontinuing AEDs. It is desirable, therefore, that AED withdrawal be completed at least 6 months before planned conception.

Contraception. All WWE must be counseled regarding contraception as they approach reproductive age. Reports of increased risk for hormonal contraceptive failure with AED use began to appear in the early 1970s. The AEDs phenobarbital, primidone, phenytoin, and carbamazepine are inducers of the hepatic cytochrome P-450 system of mixed function oxidases. Their use results in a reduction of exogenous estradiol and progesterone levels. There may also be an increase in steroid hormone binding globulins causing a decrease in free hormone levels. Both actions may result in a failure of hormonal contraception. Breakthrough bleeding may occur, although ovulation and pregnancy can result without this warning. Valproic acid/divalproex sodium inhibit the hepatic microsomal enzyme system, and the newer AEDs gabapentin, vigabatrin, and lamotrigine have no significant effect. These AEDs have not been reported to result in failure of hormonal contraception.

Levonorgestral implants do not appear to be a good alternative for contraception in WWE using enzyme-inducing AEDs. Levonorgestral is a progestin-only formulation, and its efficacy is reduced in this setting. IM medroxyprogesterone delivers higher dosages of progestin for contraception but has not yet been evaluated for effectiveness in WWE.

The effectiveness of hormonal contraception in the context of enzyme-inducing AEDs remains at approximately the same level as that of IUDs and is superior to barrier methods of birth control. Formulations containing at least 50 μg of estradiol or mestranol are more protective.

Folic acid. Low serum and red blood cell folate levels have been associated with spontaneous abortion and fetal malformations in animal models and in humans. Treatment with some AEDs, including phenytoin, carbamazepine, and barbiturates, can impair folate absorption, and there is a substantial scientific basis for the recommendation of prepregnancy and early pregnancy supplementation with folic acid for WWE during reproductive years. There is little information in the literature concerning the use of folic acid supplementation specifically referable to WWE who take AEDs. Recommendations for WWE draw on literature regarding supplementation for the general population. Studies have confirmed that folic acid supplementation reduces primary and secondary risk of neural tube defects in infants of women who do not take AEDs. Optimal dosage is unclear because study supplementation

has varied between 0.36 and 5 mg/d. It remains to be seen whether supplementation offers additional reduction in the risk of neural tube or other birth defects in WWE taking AEDs because mechanisms for teratogenesis may be different from those for women in the general population.

Seizures and hormonal fluctuations. Many women report a fluctuation in seizure frequency related to their menstrual cycle. Information from animal experiments supports the concept that estrogens lower and progestins raise the seizure threshold. Other physiologic factors and changes in serum concentrations of AEDs may contribute to altered seizure thresholds seen in WWE. The true frequency of this problem is unclear, and management strategies are unproved, reported in small, uncontrolled case series. This is an area that requires further study.

Menstrual cycle disturbances and reduced fertility are common problems for WWE and may be attributed to the seizure disorder itself or to antiepileptic medications. Neurologists caring for WWE should be aware of these issues and prepared to make appropriate endocrinology or gynecology referral. The expression of seizures in the peri- and postmenopausal woman has not been studied, and the effect of hormone replacement for postmenopausal WWE requires evaluation.

Counseling. The current level of risk for poor pregnancy outcome with optimal care for WWE does not constitute a contraindication to pregnancy. Over 90% of WWE can expect good pregnancy outcomes. A minority of WWE will experience a worsening of seizure control during pregnancy.

A coordinated approach to the care of WWE, with contributions from a primary care provider, obstetrician, geneticist, and neurologist, is ideal. Interdisciplinary communication for counseling and management is crucial. Documentation of discussions surrounding the risks of and alternatives to AED therapy as well as concerns regarding seizure occurrence during pregnancy is necessary.

As many as 40% of pregnancies in the United States are unplanned. Fifty percent of women with planned pregnancies have not consulted a health care provider before pregnancy. Many WWE will have unplanned pregnancies or will not have contact with the health care system in the first weeks of a planned pregnancy. This fact emphasizes the need for early and regular counseling of WWE during the reproductive years.

Although figures are not consistent over studies, there is a higher rate of spontaneous abortion and other complications of pregnancy in WWE. These complications are probably multifactorial. They may be secondary to AEDs, psychosocial or socioeconomic factors, or the effects of seizures on gonadotropin levels.

The incidence of birth defects is higher in the offspring of WWE than it is in women in the general population. Numerous observational studies of pregnancy outcomes in WWE, with and without controls, have been conducted. Many early studies are methodologically flawed, and AED usage patterns have changed over the past 30 years, making older studies difficult to interpret or utilize for parameter development. This body of work has, however, contributed to an understanding of the nature and scope of the problem of AED teratogenesis.

Major malformations (structural abnormalities that require surgical intervention to prevent death or significant dysfunction) occur in 2 to 3% of infants born to mothers without epilepsy. For children of WWE taking AEDs, the risk of major malformations is 4 to 6%. This increase in risk may be multifactorial, although all AEDs commonly used are associated with the occurrence of birth defects. The teratogenic potential of the newly developed AEDs is unknown. Polytherapy and higher drug dosages increase teratogenic risk. Socioeconomic and hereditary factors may also be instrumental in the development of birth defects, and the role of folate deficiency requires further clarification.

The inheritance of epilepsy is difficult to ascertain because not all recurrent seizure disorders can be etiologically classified. Retrospective studies indicate a genetic factor in some forms of epilepsy. Primary generalized seizures and maternal epilepsy increase the risk of epilepsy in the child. If the cause of epilepsy is clear, e.g., traumatic, the increased risk for epilepsy in the offspring is negligible compared with that of the general population risk of 0.7 to 1%.

WWE during and after pregnancy. AED monitoring and adjustment. The physical and psychosocial risks of potential maternal and fetal injury with convulsive seizures during pregnancy support the practices of optimizing AED therapy before pregnancy, counseling women concerning compliance, and monitoring non–protein-bound AED levels.

If seizures are well controlled with monotherapy, the AED should ordinarily be continued. Changes in AEDs during pregnancy for the purpose of reducing teratogenic risk are contraindicated for several reasons. There is risk for precipitation of seizures. Often, the advice of a physician is not sought until pregnancy has been established for several weeks, at which point there is limited advantage to change. Overlapping AEDs during change exposes the fetus to the effects of an additional AED.

Compliance with AED regimens by WWE during pregnancy may be reduced due to fears surrounding the effect of these medications on the developing fetus. Careful counseling about the potential dangers of seizures and status epilepticus for WWE and their children may bolster compliance.

There is no strong consensus or epidemiologic evidence that supports a specific frequency for clinical or AED monitoring of pregnant WWE. Although total AED levels fall throughout pregnancy, non–protein-bound (free) levels remain more constant. Automated assays that provide free AED levels are available. Total levels do not predict AED response during pregnancy and are insufficient for the ratio-

nal management of highly or moderately protein-bound AEDs in pregnant WWE. A baseline, preconception, non–protein-bound AED level repeated at the beginning of each trimester and in the last 4 weeks of pregnancy will be sufficient for women with good seizure control. More frequent determinations are indicated with increased seizure frequency or side effects, or if noncompliance is a concern. The primary indication for AED dosage or drug change remains clinical, based on seizure occurrence or adverse effects.

Vitamin K. AED therapy with enzyme-inducing agents has been shown to cause vitamin K deficiency in neonates born to WWE. The pathogenesis is unclear. It has been suggested that AEDs cross the placental barrier and induce hepatic microsomal enzymes in the fetal liver. These enzymes, in turn, may promote degradation of vitamin K in the fetus. The prenatal administration of oral vitamin K to pregnant WWE taking AEDs to prevent early (in the first 24 hours of life) hemorrhagic disease of the newborn is theoretically useful. Nonfunctional procoagulants that are decarboxylated forms of vitamin K-dependent coagulation factors have been identified in cord blood of infants born to WWE taking enzyme-inducing AEDs with significantly greater frequency than in control infants. Prenatal vitamin K_1 supplementation for WWE of 10 mg per day from the 36th week of gestation until delivery has been shown to suppress their appearance. Outcome studies are required to confirm the clinical usefulness of prenatal vitamin K supplementation. There is little or no risk related to the prenatal administration of oral vitamin K_1 to pregnant WWE. This practice does not supplant the recommendation of the AAP and the ACOG that all neonates receive vitamin K_1 at birth.

Breast-feeding. The AEDs currently in use are compatible with breast-feeding. There are no absolute contraindications to breast-feeding for WWE. There has been one report of methemoglobinemia occurring in a breast-fed infant of a WWE taking phenytoin and a case report of an infant with thrombocytopenic purpura and anemia presumed to have been induced by valproic acid through breast milk. There have been no other reports of hepatic or hematologic toxicity to breast-fed infants of WWE taking AEDs. The benefits of breast-feeding for the infant and mother are believed to outweigh the small risk of adverse effects caused by AEDs. Therefore, breast-feeding may be advocated as an option for infants of WWE.

Postpartum AED adjustment. For some women, AED dosage increases will be necessary during pregnancy. Monitoring WWE in the postpartum period, clinically and with non–protein-bound AED levels, should continue. With the reversal of physiologic changes of pregnancy, AED dosages usually may be reduced to prepregnancy levels by 8 weeks postpartum. Continuing higher AED dosages may result in toxicity.

Recommendations. The recommendations that follow are presented using the AAN QSS category definitions, the strength of which rely on classification of evidence.

WWE during reproductive years. The following recommendations are proposed as guidelines:

- The choice of AED for WWE during their reproductive years should be that deemed most appropriate for seizure type.
- Monotherapy should be the aim of treatment.
- The decrease in effectiveness of hormonal contraception observed in WWE taking enzyme-inducing AEDs must be discussed with all WWE as they enter reproductive years.
- In light of known pregnancy patterns (high rate of unplanned pregnancies and late provider contact), folic acid supplementation should be instituted in WWE with no less than 0.4 mg per day and continued through pregnancy.

The following recommendations are proposed as practice options:

- If hormonal contraception is chosen as the preferred method of birth control in a woman taking enzyme-inducing AEDs, a formulation that includes at least 50 μg of ethinyl estradiol or mestranol should be used. The risk of contraceptive failure in this setting should be discussed with WWE and the discussion documented.
- Prepregnancy counseling should include the topics listed below (additional information for patients with epilepsy and their families may be obtained from the EFA at 1-800-EFA-1000 or www.efa.org):

prepregnancy and pregnancy folic acid supplementation;

teratogenic potential of AEDs, including risk levels and discussion of major and minor birth defects;

options for considering AED discontinuation before pregnancy;

possibility for change in seizure frequency during pregnancy;

importance of medication compliance during pregnancy;

need for regular follow-up during pregnancy with AED level monitoring;

inheritance risks for seizures;

vitamin K supplementation in the last month of pregnancy; and

advantages and disadvantages of breast-feeding.

WWE during and after pregnancy. The following recommendations are proposed as guidelines:

- AED therapy for WWE should be optimized before conception if possible.

If AED withdrawal is planned, this should be completed at least 6 months before conception.

Change to an alternate AED should not be undertaken during pregnancy for the sole purpose of reducing teratogenic risk.

- WWE, especially those treated with carbamazepine, divalproex sodium, or valproic acid, should be offered prenatal testing with alpha-fetoprotein levels at 14 to 16 weeks' gestation, Level II (structural) ultrasound at 16 to 20 weeks' gestation, and, if appropriate, amniocentesis for amniotic fluid alpha-fetoprotein and acetylcholinesterase levels.
- Breast-feeding is not contraindicated in WWE taking AEDs; however, for WWE taking sedating AEDs, the neonate must be monitored for sedation.

The following recommendations are proposed as practice options:

- Non–protein-bound AED levels should be monitored during pregnancy. For the stable patient, levels should be ascertained before conception, at the beginning of each trimester, and in the last month of pregnancy. Additional levels should be done when clinically indicated (seizure occurrence, side effects, suspected noncompliance).
- AED levels should be monitored through the eighth postpartum week. If AED dosage increases have been necessary during pregnancy, subsequent reductions to the prepregnancy dosage will usually be possible and may be necessary to avoid toxicity.
- Vitamin K, 10 mg per day, should be prescribed in the last month of pregnancy to WWE taking enzyme-inducing AEDs. If this has not been done, parenteral vitamin K_1 should be administered to WWE as soon as possible after the onset of labor. Note: This recommendation does not supplant the ACOG/AAP recommendation for the administration of 1 mg vitamin K_1 to the neonate.

Recommendations for future research.

- There remains a need for well-designed studies of pregnancy outcomes for WWE, especially in light of the availability of several new AEDs.
- A study of the efficacy of hormonal contraception in WWE is needed in order that those requiring AEDs can be appropriately counseled regarding optimal birth control methods.
- Investigation of the complex issues surrounding seizure frequency changes through the stages of reproductive life and with cyclic hormonal fluctuations over the menstrual cycle is necessary.
- Further research into genetic markers that may predict a susceptibility to the teratogenic effects of AEDs may help guide primary and secondary preventive efforts.
- Ethical issues surrounding testing of AEDs in women during reproductive years must be explored and addressed.
- Endorsement and promotion of pregnancy registries to monitor AED teratogenesis should be undertaken by professional organizations of health care providers involved in the care of WWE.

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Appendix 1

Definitions for classification of evidence

Class I: Evidence provided by one or more well-designed, randomized, controlled clinical trials, including overviews (meta-analyses) of such trials.

Class II: Evidence provided by one or more well-designed, observational clinical studies with concurrent controls (e.g., case-control and cohort studies).

Class III: Evidence provided by expert opinion, case series, case reports, and studies with historical controls.

Definitions for strength of recommendations

Standard: A principle for patient management that reflects a high degree of clinical certainty (usually this requires Class I evidence that directly addresses the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).

Guideline: A recommendation for patient management that reflects moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence).

Practice option: A strategy for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion).

Practice Advisory: A practice recommendation for emerging and/or newly approved therapies or technologies based on evidence from at least one Class I study. The evidence may demonstrate only a modest statistical effect or limited (partial) clinical response, or significant cost-benefit questions may exist. Substantial (or potential) disagreement among practitioners or between payers and practitioners may exist.

Appendix 2

Quality Standards Subcommittee members: Michael K. Greenberg, MD, Co-Chair; Gary Franklin, MD, MPH, Co-Chair; Milton Alter, MD, PhD; John Calverley, MD; Robert G. Miller, MD; Jacqueline French, MD; Stephen Ashwal, MD; Jay H. Rosenberg, MD; Catherine A. Zahn, MD, Project Facilitator; James Stevens, MD; Douglas J. Lanska, MD; Shrikant Mishra, MD, MBA; Germaine L. Odenheimer, MD; and George Paulson, MD.