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SPECIAL REPORT

Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency

Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society

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Summary

A committee assembled by the American Academy of Neurology (AAN) reassessed the evidence related to the care of women with epilepsy (WWE) during pregnancy, including the risk of pregnancy complications or other medical problems during pregnancy, change in seizure frequency, the risk of status epilepticus, and the rate of remaining seizure-free during pregnancy. The committee evaluated the available evidence according to a structured literature review and classification of relevant articles. For WWE who are taking antiepileptic drugs (AEDs), there is probably no substantially increased risk (>2 times expected) of cesarean delivery or late pregnancy bleeding, and probably no moderately increased risk (>1.5 times expected) of premature contractions or premature labor and delivery. There is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy for WWE who smoke. WWE should be counseled that seizure freedom for at least 9 months prior to pregnancy is probably associated with a high likelihood (84–92%) of remaining seizure-free during pregnancy. WWE who smoke should be counseled that they possibly have a substantially increased risk of premature contractions and premature labor and delivery.

KEY WORDS: Guideline, Pregnancy, Epilepsy, Seizure, Complications.

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Recent estimates of the U.S. population (United States Department of Health and Human Services, 2007) and the prevalence of epilepsy (Hirtz et al., 2007) indicate that

approximately one-half million women with epilepsy (WWE) are of childbearing age. It has also been estimated that 3–5 births per thousand will be to WWE (Yerby, 2000). Epilepsy is defined by the presence of recurrent, unprovoked seizures, and the treatment is typically a daily, long-term antiepileptic drug (AED) regimen. The majority of people with epilepsy have well-controlled seizures, are otherwise healthy, and, therefore, expect to participate fully in life experiences, including child-bearing.

This parameter and the two companion parameters are updates of the previous practice parameter from 1998 (American Academy of Neurology, 1998). They employ improved methodology for the development of practice parameters to analyze a large number of new studies informing the clinical management of WWE who are pregnant or plan pregnancy.

This parameter summarizes evidence for two broad clinical questions:

Compared to women without epilepsy, are WWE at increased risk for pregnancy-related complications, including (1) cesarean delivery; (2) preeclampsia; (3) pregnancy-induced hypertension; (4) premature contractions or premature labor and delivery; (5) bleeding complications; and (6) spontaneous abortion?

For WWE who become pregnant, what is the risk of epilepsy-related complications during pregnancy, including (1) change in seizure frequency, (2) risk of status epilepticus, and (3) chance of recurrent seizures if WWE are seizure-free for 9 months prior to pregnancy?

Description of the Analytic Process

Panel formation

The American Academy of Neurology (AAN) assembled a panel of experts including epileptologists, general neurologists, and doctors in pharmacy with expertise in AEDs. Panel members with expertise in obstetrics, obstetrical nursing, and teratology were also included. This effort was supported by a grant from the Milken Family Foundation.

Literature review and article selection

A literature search was performed using MEDLINE, MEDLINE-In-Process, Current Contents, Biological Abstracts, and BIOSIS previews for relevant articles published between 1985 and December 2005. An updated search was performed from December 2005 through June 2007, with manual searches on some topics through February 2008. The arbitrary cutoff date of 1985 was chosen because these relatively recent articles were thought to reflect current practice and AED usage patterns and, therefore, be more applicable and reliable for this assessment than earlier reports. The search terms used were seizures/epilepsy, catamenial epilepsy, pregnancy, anticonvulsants, antiepileptic drugs, teratogenesis, birth defects, pregnancy registry, cognitive outcome, vitamin K, folate/folic acid, breastfeeding, oral contraceptives, polycystic ovary syndrome, hormone replacement therapy, menopause, perimenopause, and fertility. The search was confined to articles using human subjects and included all languages for which there was an abstract in English. A secondary search for missed references was done by reviewing the bibliographies of review articles and meta-analyses identified in the primary search.

The literature search yielded a total of 876 abstracts. To find relevant articles, two panel members screened each of the abstracts. If either panel member thought the article was potentially relevant, the full text was obtained for review. In general, abstracts were excluded from further analysis if they related to eclampsia rather than seizures due to epilepsy, related to basic mechanisms such as teratogenesis or placental AED metabolism, or were unrelated to the questions posed by the panel.

From the abstracts, a total of 285 were selected for complete review. Four panel members reviewed the full text of the articles and identified those that were relevant to each clinical question. Articles were included in the analysis of this paper if they determined the frequency of pregnancy-related or epilepsy-related complications in a cohort of pregnant WWE. Articles relevant to the clinical questions of the companion articles were included in the appropriate article and are described there.

Study classification and measures of effect

With the exception of the question pertaining to recurrent seizures in seizure-free WWE, articles were classified according to the AAN prognostic classification of evidence scheme (see Appendix S4a). Articles regarding recurrent seizures in seizure-free WWE were classified according to the AAN screening classification-of-evidence scheme (see Appendix S4b). This scheme was chosen because the absolute risk of seizure recurrence, rather than the relative risk, was deemed most clinically relevant to this question. Articles were classified separately by four panel members. Disagreements on categorization of the articles were resolved by discussion and consensus.

For pregnancy-related complications, studies were given a lower class of evidence when they did not compare complication frequencies in pregnant WWE to pregnant women without epilepsy. For epilepsy-related complications, studies were given a lower class of evidence when they did not compare complication frequencies in pregnant WWE to nonpregnant WWE.

In addition, studies were downgraded for a lack of masked outcome assessment or if they provided insufficient information to determine relative risk (RR) or odds ratios (ORs). The requirement for masked outcome assessment was waived for obviously objective outcomes such

as cesarean delivery, preeclampsia, pregnancy-induced hypertension, spontaneous abortion, and status epilepticus. Meta-analyses were not performed due to heterogeneity of the studies.

When possible, the associations between epilepsy and pregnancy-related complications or pregnancy and epilepsy-related complications were determined using ORs. If not reported in the article, the writing panel attempted to calculate the appropriate ORs. For the only Class I article (Viinikainen et al., 2006), the authors were personally contacted to provide further detail on data reported in the article. To allow calculation of the OR when one of the cells of the two-by-two table was zero, 0.5 was added to each cell (Yusuf et al., 1985).

For the purposes of this parameter, a ''moderately'' increased risk is defined by an OR of >1.5 and <2.0 and a ''substantially'' increased risk by an OR of 2.0 or greater.

The 95% confidence intervals (CIs) of the ORs were used as the measure of precision. Negative studies were judged to be sufficiently sensitive to exclude an increased risk based on the upper limit of the 95% CIs. Therefore, a study failing to show a significant increased risk of a complication based on an OR of 1.2 with 95% CIs of 0.6–1.7 would be judged to be too insensitive to exclude a moderately increased risk of the complication. The strength of the practice recommendations was linked directly to the class of evidence using the scheme described in Appendix S5.

Analysis of Evidence

Do WWE have an increased risk of pregnancy-related complications?

Twenty-five articles met inclusion criteria for pregnancy-related complications in WWE. Several articles included information pertinent to more than one question. Of these 25 articles, nine were graded Class III or higher (Table S1).

Cesarean delivery

One Class I study (Viinikainen et al., 2006) did not show a significant increased risk of cesarean delivery in WWE taking AEDs compared to women without epilepsy (OR 1.04, 95% CI 0.71–1.52). A Class II study (Richmond et al., 2004) did not show a significant increased risk of cesarean delivery in WWE compared to women without epilepsy (OR 1.24, 95% CI 0.99–1.55). However, both studies were insufficiently sensitive to exclude a moderately increased risk.

Three Class III studies [OR 17.88, 95% CI 4.73–67.58 (Laskowska et al., 2001); OR 1.58, 95% CI 1.10–2.25 (Olafsson et al., 1998); and OR 2.2, 95% CI 1.42–3.41 (Sawhney et al., 1996)] demonstrated a significant substantial increased risk.

Other than the increased risk of bias and statistical imprecision of some studies, there is little information to explain the increased cesarean delivery rate observed in the Class III studies compared to the Class I and II studies.

Conclusion

Based on evidence from one Class I and one Class II study, it is probable that WWE taking AEDs do not have a substantially increased risk of cesarean delivery. Because of the lack of statistical precision in the Class I and Class II studies and the evidence from multiple Class III studies, a moderately increased risk of cesarean delivery is possible.

Preeclampsia

One Class I study (Viinikainen et al., 2006) did not show a significant increased risk of preeclampsia in WWE taking AEDs compared to women without epilepsy (OR 1.4, 95% CI 0.66–3.15). However, this study was insufficiently sensitive to exclude an increased risk.

Two Class II studies [RR = 0.8, 95% CI 0.2–2.9 (Hiilesmaa et al., 1985) and OR 1.24, 95% CI 0.77–1.99 (Richmond et al., 2004)] did not observe a significant increase in the risk of preeclampsia in WWE compared to women without epilepsy. These studies were insufficiently sensitive to exclude an increased risk.

Conclusion

There is insufficient evidence to support or refute an increased risk of preeclampsia in WWE taking AEDs.

Pregnancy-induced hypertension

One Class II study [OR 1.4, 95% CI 1.1–1.9 (Richmond et al., 2004)] showed an increased risk of pregnancy-induced hypertension in WWE as compared to woman without epilepsy. Another Class II study [OR 0.7, 95% CI 0.3–1.6 (Hiilesmaa et al., 1985)] showed no significant increased risk but was insufficiently sensitive to exclude a moderately increased risk.

Two Class III studies [OR 7.8, 95% CI 0.8–76.9 (Laskowska et al., 2001) and OR 1.2, 95% CI 0.7–2.1 (Sawhney et al., 1996)] demonstrated no significant increased risk. These studies were insufficiently sensitive to exclude a substantially increased risk.

Conclusion

Based on results from two conflicting Class II studies, there is insufficient evidence to support or refute an increased risk of pregnancy-induced hypertension in WWE.

Premature contractions and premature labor and delivery

One Class I study (Viinikainen et al., 2006) showed no substantially increased risk of premature contractions or premature labor and delivery in WWE taking AEDs compared to control women without epilepsy (OR 0.51, 95% CI 0.19–1.36).

One Class II study (Hvas et al., 2000) showed an increased risk for WWE who were smokers compared to control women who were also smokers (OR 3.4, 95% CI 1.8–6.5) (data not given for all WWE compared to controls). One Class III study (Wilhelm et al., 1990) also showed an increased risk ($p < 0.05$). Another Class III study (Laskowska et al., 2001) demonstrated no significant increased risk but was insufficiently sensitive to exclude a substantially increased risk (OR 8.24, 95% CI 0.92–70.32). A Class III study (Hiilesmaa et al., 1985) showed no significant increased risk but was not sufficiently sensitive to exclude an increased risk (RR 0.7, 95% CI 0.3–1.4). In a categorical, chi-square statistic, it was reported that the rates of premature births were not different than controls ($p = 0.3$) (Olafsson et al., 1998), and another study found no differences in gestational ages in the offspring of WWE compared to controls [WWE = 38.06, standard deviation (SD) 1.42 vs. controls = 38.17, SD 3.58 weeks] (Sawhney et al., 1996).

Conclusions

Based on evidence from one Class I study, it is probable that WWE taking AEDs do not have a moderately increased risk of premature contractions and premature labor and delivery during pregnancy. However, based on evidence from one Class II study, it is possible that WWE who smoke do have a substantially increased risk of premature contractions and premature labor and delivery during pregnancy compared to women without epilepsy who smoke.

Pregnancy-related bleeding complications

One Class I study (Viinikainen et al., 2006) did not show a significant increased risk of late pregnancy bleeding in WWE taking AEDs compared to women without epilepsy (OR 1.18, 95% CI 0.70–1.97). One Class III study (Hiilesmaa et al., 1985) also demonstrated no increased risk (RR 0.9, 95% CI 0.4–2.0). However, neither study was sufficiently sensitive to exclude a moderately increased risk.

Conclusion

Based on evidence from one Class I and one Class III study, it is probable that WWE taking AEDs do not have a substantially increased risk of late pregnancy-related bleeding complications. However, because of a lack of statistical precision in these studies, a moderately increased risk cannot be excluded.

Spontaneous abortion

One Class III study (Martin & Millac, 1993) showed a decreased risk of spontaneous abortion in WWE compared to controls (6.9% vs. 7.5%). No denominator is provided for the control group to allow calculation of ORs.

Conclusion

Data are inadequate to support or refute an increased risk of spontaneous abortion in WWE.

Do WWE have an increased risk of epilepsy-related complications during pregnancy?

Twenty-five articles met inclusion criteria for epilepsy-related complications in pregnant WWE.

Change in seizure frequency

No study compared the change in seizure frequency in pregnant WWE to nonpregnant WWE; therefore, an appropriate ''gold standard'' comparator group was not available. Hence, all studies were graded Class IV (Table S2). Three articles (Bardy, 1987; Gjerde et al., 1988; Tomson et al., 1994) used each patient's nonpregnant seizure frequency (per pregnancy) as its own control. In one study, which evaluated 154 pregnancies (Bardy, 1987), seizure frequency was unchanged in 54% (95% CI 0.46–0.62) [including 48 (31%) seizure-free patients], decreased in 14% (95% CI 0.10–0.21), and increased in 32% (95% CI 0.25–0.40) compared to prepregnancy seizure frequency. In this study, AED doses were increased when seizure frequency increased.

In another study, which evaluated 78 pregnancies (Gjerde et al., 1988), seizure frequency was unchanged in 72% (95% CI 0.61–0.81) for ''major szs'' (Wilcoxon test $p > 0.50$ for significant differences), decreased in 14% (95% CI 0.08–0.24), and increased in 14% (95% CI 0.08–0.24) compared to prepregnancy baseline. AED doses were increased when seizure frequency increased in this study as well.

In a third Class IV study, which evaluated 93 pregnancies (Tomson et al., 1994), seizure frequency as a whole was not different in pregnancy compared to baseline ($p = 0.42$). The exact numbers were not provided, but the percent change was reported as the following: 61% unchanged, 24% decreased, 15% increased. Seizure increase was more likely in partial epilepsy (29%) than in idiopathic epilepsy (7%). AED doses were unchanged in this study.

Another Class IV study (Otani, 1985) used both retrospective recall and postpartum prospective seizure frequency as comparators. In this study of 74 AED-compliant patients, seizure frequency was unchanged in 80% (95% CI 0.69–0.87), decreased in 4% (95% CI 0.01–0.11), and increased in 16% (95% CI 0.01–0.26). AED doses were unchanged in this study.

A report of another study (Tanganelli & Regesta, 1992) used postpartum seizure frequency as a comparator. In this study of 138 pregnancies, seizure frequency was unchanged in 80% (95% CI 0.72–0.86), decreased in 3% (95% CI 0.01–0.07), and increased in 17% (95% CI 0.12–0.25). The AED management was not stated in this study.

The percentage of patients with unchanged seizure frequency in these studies ranged from 54–80%. The highest rate of unchanged seizure frequency was the 80% reported in AED-compliant patients, documented

by serum levels (Otani, 1985). The rate of seizure decrease ranged from 3–24%. The rate of seizure increase ranged from 14–32%.

Unfortunately, none of these studies included an appropriate nonpregnant WWE comparator group to provide information on the natural stability of seizure frequency among WWE. Without this information, it is impossible to determine if the changes in seizure frequency observed were related to the pregnancy itself.

Conclusion

There is insufficient evidence to determine the change in seizure frequency in pregnant WWE.

Status epilepticus

No studies compared the risk of status epilepticus in nonpregnant WWE to pregnant WWE. Hence, all studies were graded Class IV (Table S3). Three population-based studies reported a frequency of status epilepticus in WWE during pregnancy of 0–1.3% [0/154, 0%, 95% CI 0.00–0.3 (Bardy, 1987); 1/78 convulsive status epilepticus, 1.3%, 95% CI 0.00–0.07 (Gjerde et al., 1988); and 0/89, 0%, 95% CI 0.00–0.04 (Tomson et al., 1994)]. Similarly, a large prospective, but not population-based, study of nearly 2,000 pregnancies (EURAP Study Group, 2006) found status epilepticus in 36/1,956 (1.8%, 95% CI 0.01–0.03) pregnancies. Twelve of these 36 episodes of status epilepticus were convulsive and 24 were nonconvulsive.

Although there is no accurate information in a similar population of persons with epilepsy to use as a historical comparator, these estimates closely approximate an annual frequency of 1.6% for status epilepticus reported in a large series of patients with varied epilepsy types (Janz, 1969). This comparison suggests status epilepticus does not occur more frequently during pregnancy. However, the absence of a comparison group of nonpregnant WWE within these studies makes it impossible to determine the relative risk of status epilepticus during pregnancy.

Conclusion

There is insufficient evidence to support or refute an increased risk of status epilepticus in pregnant WWE.

Seizure recurrence in previously seizure-free WWE

Two Class II articles (Gjerde et al., 1988; Tomson et al., 1994) showed that for WWE who were seizure-free for 9 months prior to pregnancy, 84–92% remained seizure-free during pregnancy (Table S4). In one study, 38 of 45 (84%; CI 0.71–0.92) of pregnant WWE remained seizure-free (Gjerde et al., 1988), and in the other study, 47 of 51 (92%; CI 0.82–0.97) of pregnant WWE remained seizure-free (Tomson et al., 1994).

One larger Class III article (Vajda et al., 2008) showed that 80% of a group of WWE (n = 450) who were seizure-free at least 1 year prior to pregnancy remained seizure-free during pregnancy (exact number not provided). One Class III article showed that of 72 WWE who were seizure-free for 10 months, 74% (95% CI 0.62–0.82) remained seizure-free during pregnancy (Otani, 1985). A second Class III article showed that of 54 WWE who were seizure-free for 9 months, 94% (95% CI 0.85–0.98) remained seizure-free during pregnancy, and of 48 WWE who were seizure-free for 1 year, 92% (95% CI 0.80–0.98) remained seizure-free during pregnancy (Tanganelli & Regesta, 1992). These results are all fairly consistent across the Class of evidence and sample size of the studies.

Conclusion

Two Class II articles show that the rate of remaining seizure-free during pregnancy if WWE are seizure-free for at least 9 months to 1 year prior to pregnancy is probably 84–92%.

Recommendations

Counseling of WWE who are pregnant or are contemplating pregnancy should reflect the following:

- there is probably no substantially increased risk (>2 times expected) of cesarean delivery for WWE taking AEDs (Level B). However, there is possibly a moderately increased risk (up to 1.5 times expected) of cesarean delivery for WWE taking AEDs (Level C).
- there is probably no substantially increased risk (>2 times expected) of late pregnancy bleeding for WWE taking AEDs (Level B).
- there is probably no moderately increased risk (>1.5 times expected) of premature contractions or premature labor and delivery for WWE taking AEDs (Level B).
- there is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy for WWE who smoke (Level C).
- seizure freedom for at least 9 months prior to pregnancy is probably associated with a high likelihood (84–92%) of remaining seizure-free during pregnancy (Level B).
- there is insufficient evidence to support or refute an increased risk of preeclampsia, pregnancy-related hypertension, spontaneous abortion, a change in seizure frequency, or status epilepticus (Level U).

Clinical Context

Some of the most important findings of this practice parameter are what they do not demonstrate. There was no conclusive evidence of an increased risk of many obstetrical complications often discussed as associated with WWE during pregnancy. This raises the possibility that there is no true difference in the rates of obstetrical complications in WWE compared to the general population.

Furthermore, the findings do not suggest high rates of seizure increase or status epilepticus during pregnancy or

an increased risk of seizure relapse during pregnancy for WWE who are seizure-free. The data available to determine how seizure-free WWE fare during pregnancy indicate that it is likely that they will remain seizure-free, providing practitioners with another reason to strive for seizure freedom in their patients who are planning pregnancy.

It is hoped that this information will herald a new outlook about how high (or low) the actual risk is for health complications in WWE who become pregnant, and may serve to decrease the anxiety and perhaps the stigma produced by this clinical situation for both patient and practitioner.

Recommendations for Future Research

Stronger evidence is needed to determine if there are increased risks of preeclampsia, pregnancy-induced hypertension, and spontaneous abortion for WWE. These risks should be evaluated in large, prospective studies using well-matched control groups. The effect of specific AEDs on obstetrical outcomes also remains unexplored and deserves further study. The existing databases for evaluating the outcomes of pregnancies exposed to AEDs could potentially provide a source for such information. Further evaluation for the risks of seizure increase during pregnancy should be done, using prospective baseline information when possible. This type of analysis would help to reveal more information about the causes of seizure increase during pregnancy, which may be more complicated than AED noncompliance, decreased levels due to pregnancy metabolism, or lack of sleep. For example, the effect of the hormonal changes during pregnancy on seizure frequency could be evaluated in a careful, prospective study.

Disclaimer

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician who is caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

The findings and conclusions in the report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Disclosure: The authors report the following conflicts of interest:

Dr. Harden has served on the scientific advisory board of Cyberonics, GlaxoSmithKline, UCB Pharma, Valeant, and SK Pharmaceuticals and on the speakers' bureau of GlaxoSmithKline, Pfizer, UCB Pharma, and Abbott. She serves as an editor of *Epilepsy Currents* and receives publishing royalties from Elsevier. Dr. Harden has received research funding from Forest, UCB Pharma, Ortho McNeil, and NIH/NINDS. Dr. Harden sees women with epilepsy in her office practice.

Dr. Hopp receives royalties from UpToDate.com electronic medical journal. She has been on the speakers' bureau of UCB Pharma and GlaxoSmithKline. Dr. Hopp has given testimony in a medico-legal case.

Dr. Ting served on the scientific advisory board of UCB Pharma and has received honoraria from the Epilepsy Foundation of America.

Dr. Pennell has served on the Expert Panel for the Keppra Pregnancy Registry sponsored by UCB Pharma. She has received funding for travel from the Northeast Regional Epilepsy Group for speaking at their 2008 Epilepsy Symposium, by the UK Research Council for speaking at the Epilepsy Research UK International Expert Workshop, by UCB Pharma for attending the Executive Panel meeting for the Pregnancy Registry, by the American Epilepsy Society for attending the Board of Directors' Meeting, by the Epilepsy Foundation for attending the Board of Directors' and orientation meetings, by the Long Island Jewish Hospital for lecturing at Neurology Grand Rounds, by Duke University for lecturing at Neurology Grand Rounds, by Brigham and Women's Hospital for lecturing at the Epilepsy Research Conference, by the Milken foundation for attending Pregnancy Registry meetings, and by Massachusetts General Hospital for speaking at the Annual Teratogens Course. She has received honoraria from Journal Watch Neurology for a contributing article, paid for by Massachusetts Medical Society, NEJM, for review for the Lancet Neurology, the Northeast Regional Epilepsy group for speaking at 2008 Epilepsy Symposium, North Shore Long Island Jewish Health system, Duke University, University of Maryland, the Massachusetts General Hospital for speaking at the postgraduate course in Human Teratogens, and the AAN for speaking and directing annual courses. Dr. Pennell has served as a contributing editor for *Epilepsy Currents* and is on the editorial board of *Epilepsia*. Dr. Pennell has received research support from UCB Pharma, Marinus Pharmaceuticals, NIH, HINDS, NIMH, CDC, and Emory University Research Council.

Dr. French has served on the scientific advisory board of UCB Pharma, Johnson and Johnson, Eisai, Novartis, Valeant, Icagen, Intranasal, Sepracor, and Marinus. She has received funding for travel to present findings or give lectures from UCB Pharma, Kyowa, Eisai, Johnson and Johnson, Valeant, and GlaxoSmithKline. She has served as an associate editor for *Epilepsy Currents* and supplement editor for *Epileptic Disorders*. Dr. French is the president of the Epilepsy Study Consortium, which receives money from multiple pharmaceutical companies (including GlaxoSmithKline, UCB Pharma, Johnson and Johnson, Cyberonics, Schwarz Pharma, Ortho McNeil, Eisai, Jazz Pharmaceuticals, Ovation Pharmaceuticals, Endo Pharmaceuticals, Bial Pharmaceuticals, Neurovista, Valeant Pharmaceuticals, Icagen, Supernus, Intranasal, SK Pharmaceuticals, Taro Pharmaceuticals, Neurotherapeutics, Sepracor, and Novartis) and she consults on behalf of the consortium. Dr. French has

received research funding from Johnson and Johnson, Eisai, UCB Pharma, SK Pharmaceuticals, Valeant, Pfizer, NIH, and Epilepsy Research Foundation.

Dr. Hauser has served on the scientific advisory board of Ovation and Valeant. He has served on the editorial board of *Acta Neurologica Scandinavia, Neuroepidemiology*, and *Epilepsy Research*. He has received honoraria from Cornell University Symposium on epilepsy and acted as a consultant to Pfizer. Dr. Hauser has received research support from AAMC/CDC, NIH/NINDS, FAA, Mayo Clinic, Hotchkiss Neurological Institute, and has given expert testimony in his role as an FAA consultant.

Dr. Wiebe serves on the editorial board of *Neurology, Epilepsia, Epilepsy and Behavior*, and *Canadian Journal of Neurological Sciences.*

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Dr. Koppel reports no disclosures.

Dr. Kaplan has served on the speakers' bureau of UCB Pharma, GSK, and Ortho McNeil. He serves as an associate editor for *Neurophysiologie Clinique, Journal of Clinical Neurophysiology*, and *Epilepsia*. He received royalties from Demos Publications for the books *Neurological Disease in Women, Epilepsy A to Z, Imitators of Epilepsy*, and *Nonconvulsive Status Epilepticus*. He has received speaker honoraria from Medical College of South Carolina, Duke University, and Medical College of Virginia, has received research funding from NIH, Schwarz, Ortho McNeil, and Pfizer, and has acted as a consultant for Schering-Plough and Infinite Biological Technologies.

Dr. Robinson reports no disclosures.

Dr. Gidal has served on the scientific advisory board for GlaxoSmithKline, UCB Pharma, and Abbott Labs and served as an editor for *Epilepsy & Behaviour*, *Ann Pharmacotherapy*, and *Pharmacists letter.* Dr. Gidal has received research support from UCB Pharma.

Dr. Hovinga estimates less than 10% of his clinical effort is spent on pharmacology consults.

Dr. Wilner has served on the scientific advisory board of and received funding for travel from GlaxoSmithKline. He receives royalties from Demos Publications for *Epilepsy: 199 Answers* and *Epilepsy in Clinical Practice*. He receives board of directors compensation from GlaxoSmithKline.

Dr. Vazquez has served on the scientific advisory board of Eisai, UCB, GSK, and Ortho McNeil. She has received honoraria from UCB, GSK, Ortho McNeil, and Eisai. Dr. Vazquez has served on a speakers' bureau for Eisai, GSK, Ortho McNeil, UCB, and Novartis.

Dr. Holmes has received research funding from Abbott Labs, GlaxoSmithKline, Eisai, Novartis, Ortho McNeil, and Pfizer.

Dr. Krumholz has served on the Department of Transportation Expert Panel on Commercial Drivers and Epilepsy and has served on the editorial board of *The Neurologist* and *Clinical EEG and Neuroscience.* He has received honoraria from the Robert Wood Johnson Medical School for grand rounds.

Dr. Finnell has served on the scientific advisory board of the NEAD study at Emory University, the University of Houston Center for Life Sciences Technology, the NIH, and the NIEHS National Advisory Environmental Health Sciences Council. He has received funding for travel from Fundacion BBVA, NIEHS National Advisory Environmental Health Sciences Council, IKMC Steering Committee, European Epilepsy Meeting, NIH, and AES. Dr. Finnell has served as a journal editor for *Birth Defects Research Part A* and holds a patent on folate receptor autoantibody assay. He has received honoraria from McGill University-Montreal Neurological Institute and has received research funding from the Centers for Disease Control and Prevention for the National Birth Defects Prevention Study and the Methodist Hospital Research Institute. Dr. Finnell has given expert testimony, prepared affadavits, and acted as a witness regarding legal proceedings related to the topic of this manuscript.

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References

American Academy of Neurology. (1998) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: management issues for women with epilepsy (summary statement). *Neurology* 51:944–948.

Bardy AH. (1987) Incidence of seizures during pregnancy, labor and puerperium in epileptic women: a prospective study. *Acta Neurol Scand* 75:356–360.

EURAP Study Group. (2006) Seizure control and treatment in pregnancy. *Neurology* 66:354–360.

Gjerde IO, Strandjord RE, Ulstein M. (1988) The course of epilepsy during pregnancy: a study of 78 cases. *Acta Neurol Scand* 78:198–205.

Hiilesmaa VK, Bardy A, Teramo K. (1985) Obstetric outcome in women with epilepsy. *Am J Obstet Gynecol* 152:499–504.

Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. (2007) How common are the ''common'' neurologic disorders? *Neurology* 68:326–337.

Hvas CL, Henriksen TB, Ostergaard JR, Dam M. (2000) Epilepsy and pregnancy: effect of antiepileptic drugs and lifestyle on birth weight. *Br J Obstet Gynaecol* 107:896–902.

Janz D. (1969) *Die Epilepsien. Spezielle pathologie und therapie*. Georg Thieme Verlag, Stuttgart.

Laskowska M, Leszczyriska-Gorzelak B, Oleszczuk J. (2001) Pregnancy in women with epilepsy. *Gynecol Obstet Invest* 51:99–102.

Martin PJ, Millac PAH. (1993) Pregnancy, epilepsy, management and outcome: a 10-year perspective. *Seizure* 2:277–280.

Olafsson E, Hallgrimsson JT, Hauser WA, Ludvigsson P, Gudmundsson G. (1998) Pregnancies of women with epilepsy: a population-based study in Iceland. *Epilepsia* 39:887–892.

Otani K. (1985) Risk factors for the increased seizure frequency during pregnancy and puerperium. *Folia Psychiatr Neurol Jpn* 39:33–41.

Richmond JR, Krishnamoorthy P, Andermann E, Benjamin A. (2004) Epilepsy and pregnancy: an obstetric perspective. *Am J Obstet Gynecol* 190:371–379.

Sawhney H, Vasishta K, Suri V, Khunnu B, Goel P, Sawhney IMS. (1996) Pregnancy with epilepsy – a retrospective analysis. *Int J Gynaecol Obstet* 54:17–22.

Tanganelli P, Regesta G. (1992) Epilepsy, pregnancy, and major birth anomalies: an Italian prospective, controlled study. *Neurology* 42 (4 Suppl 5):89–93.

Tomson T, Lindbom U, Ekqvist B, Sundqvist A. (1994) Epilepsy and pregnancy: a prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. *Epilepsia* 35:122–130.

United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Bridged-Race Population Estimates, United States. (2007) July 1st resident population by state, county, age, sex, bridged-race, and Hispanic origin on CDC WONDER On-line Database. http://wonder.cdc.gov.

Vajda FJE, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. (2008) Seizure control in antiepileptic drug-treated pregnancy. *Epilepsia* 49:172–175.

Viinikainen K, Heinonen S, Eriksson K, Kalviainen R. (2006) Community-based, prospective, controlled study of obstetric and neonatal outcomes of 179 pregnancies in women with epilepsy. *Epilepsia* 47:186–192.

Wilhelm J, Morris D, Hotham N. (1990) Epilepsy and pregnancy – a review of 98 pregnancies. *Aust NZ J Obstet Gynaecol* 30:290–295.

Yerby MS. (2000) Quality of life, epilepsy advances, and the evolving role of anticonvulsants in women with epilepsy. *Neurology* 55:S21–S31.

Yusuf S, Peto R, Lewis J, Collins R, Sleight P. (1985) Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 27:335–371.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix e-1a. Mission statement of Quality Standards Subcommittee.

Appendix e-1b. Mission statement of Therapeutics and Technology Assessment Subcommittee.

Appendix e-2. Conflict of interest statement.

Appendix e-3a. Quality Standards Subcommittee (QSS) members.

Appendix e-3b. Therapeutics and Technology Assessment Subcommittee members.

Appendix e-4a. Classification of evidence for rating of a prognostic article.

Appendix e-4b. Classification of evidence for rating of a screening article.

Appendix e-5. Classification of recommendations.

Table e-1. Adverse pregnancy outcomes

Table e-2. Change in seizure frequency during pregnancy (95% confidence intervals calculated by committee)

Table e-3. Rate of status epilepticus (SE) (95% confidence intervals calculated by committee)

Table e-4. Rate of remaining seizure-free (95% confidence intervals calculated by committee)

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