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Practice Parameter update: Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding

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

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ABSTRACT

Objective: To reassess the evidence for management issues related to the care of women with epilepsy (WWE) during pregnancy, including preconceptional folic acid use, prenatal vitamin K use, risk of hemorrhagic disease of the newborn, clinical implications of placental and breast milk transfer of antiepileptic drugs (AEDs), risks of breastfeeding, and change in AED levels during pregnancy.

Methods: A 20-member committee evaluated the available evidence based on a structured literature review and classification of relevant articles published between 1985 and October 2007.

Results: Preconceptional folic acid supplementation is possibly effective in preventing major congenital malformations in the newborns of WWE taking AEDs. There is inadequate evidence to determine if the newborns of WWE taking AEDs have a substantially increased risk of hemorrhagic complications. Primidone and levetiracetam probably transfer into breast milk in amounts that may be clinically important. Valproate, phenobarbital, phenytoin, and carbamazepine probably are not transferred into breast milk in clinically important amounts. Pregnancy probably causes an increase in the clearance and a decrease in the concentration of lamotrigine, phenytoin, and to a lesser extent carbamazepine, and possibly decreases the level of levetiracetam and the active oxcarbazepine metabolite, the monohydroxy derivative.

Recommendations: Supplementing women with epilepsy with at least 0.4 mg of folic acid before they become pregnant may be considered (Level C). Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered (Level B) and monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels may be considered (Level C). A paucity of evidence limited the strength of many recommendations. *Neurology*® 2009;73:142–149

GLOSSARY

AAN = American Academy of Neurology; **AED** = antiepileptic drug; **CBZ** = carbamazepine; **CI** = confidence interval; **ESM** = ethosuximide; **GBP** = gabapentin; **LTG** = lamotrigine; **LVT** = levetiracetam; **MHD** = monohydroxy derivative; **OR** = odds ratio; **OXC** = oxcarbazepine; **PB** = phenobarbital; **PHT** = phenytoin; **PRM** = primidone; **TPM** = topiramate; **VPA** = valproate; **WWE** = women with epilepsy.

Recent estimates of the US population[1] and the prevalence of epilepsy[2] indicate that approximately one-half million women with epilepsy (WWE) are of childbearing age. It has also been estimated that three to five births per thousand will be to WWE.[3] 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 childbearing.

This parameter summarizes evidence for six important questions relating to the clinical management of WWE who are pregnant or plan pregnancy:

1. Does preconceptional folic acid supplementation reduce the risk of birth defects in neonates of WWE taking AEDs?
2. What is the risk of hemorrhagic disease in neonates born to WWE taking AEDs?
3. Does prenatal vitamin K supplementation reduce the risk of hemorrhagic disease in the newborns of WWE taking AEDs?
4. Do maternally ingested AEDs cross the placenta or penetrate into breast milk?
5. Does indirect exposure to maternally ingested AEDs increase the risk of symptomatic effects in the newborn?
6. Are there changes in AED levels during pregnancy in WWE?

DESCRIPTION OF THE ANALYTIC PROCESS
The panel formation, literature search strategy, and literature analytic process are described in the companion article on WWE and obstetrical complications and seizure change.[4]

ANALYSIS OF EVIDENCE
Does preconceptional folic acid supplementation reduce the risk of birth defects in neonates of WWE taking AEDs? To be included in the analysis, articles had to measure the association between preconceptional folic acid use and the outcome of major congenital malformations (MCMs). MCMs were defined as structural abnormalities with surgical, medical, or cosmetic importance.[5] The development of an MCM was considered an objective outcome.

Eleven articles relevant to this question were identified by the literature search. The articles were rated according to the American Academy of Neurology (AAN) classification of therapeutic evidence scheme (see appendix e-4A on the *Neurology*® Web site at www.neurology.org). Six studies were graded Class IV and are not discussed further. The remaining studies were rated Class III (see table e-1).

Among the five Class III articles, one study (n = 156) showed an increased risk of MCMs with lack of folic acid supplementation (odds ratio [OR] 16.88, 95% confidence interval [CI] 4.79–59.52).[6] The folic acid supplementation dose in this study was reported as 2.5–5 mg per day. A second Class III study measured a significant association between serum folic acid concentrations <4.4 nmol/L and neonatal malformation (adjusted OR 5.8, 95% CI 1.3–27, $p = 0.02$).[7]

Several Class III studies failed to show an association between folic acid and MCMs but were insuffi-ciently sensitive to exclude a substantial risk reduction from folic acid supplementation. One study reported an OR of 1.67 for MCMs in the off-spring of mothers on valproate (VPA) who were not taking folic acid supplementation. However, the result was not significant (95% CI 0.62–4.50).[8] bxAn-other study showed no effect of folic acid supplementation (OR 0.86, 95% CI 0.34–2.15),[9] but lacked the statistical precision to exclude a potential benefit. The final study[10] was inconclusive since all WWE who had offspring with MCMs had folic acid supplementation.

Conclusion. The risk of MCMs in the offspring of WWE is possibly decreased by folic acid supplementation (two adequately sensitive Class III studies).

Recommendation. Preconceptional folic acid supplementation in WWE may be considered to reduce the risk of MCMs (Level C).

Clinical context. Folic acid supplementation is generally recommended to reduce the risk of MCMs during pregnancy,[11] and although the data are insufficient to show that it is effective in WWE, there is no evidence of harm and no reason to suspect that it would not be effective in this group. Therefore, the strength of this evidence should not impact the current folic acid supplementation recommendation that all women of childbearing potential, with or without epilepsy, be supplemented with at least 0.4 mg of folic acid daily prior to conception and during pregnancy.[12] There was insufficient published information to address the dosing of folic acid and whether higher doses offer greater protective benefit to WWE taking AEDs.

What is the risk of hemorrhagic disease in neonates born to WWE taking AEDs? To be included in the analysis, studies had to compare the risk of neonatal hemorrhagic complications in newborns of WWE taking AEDs to newborns of women without epilepsy. Hemorrhagic complications were defined as any hemorrhage within 24 hours of birth. Studies looking solely at surrogate markers of bleeding risk such as coagulation factor levels were excluded. The risk of bias in each study was measured using the AAN prognostic classification of evidence scheme (appendix e-4B).

Ten articles were identified by the literature search. All but two articles were rated Class IV. The remaining two articles, one Class II and one Class III, are summarized in table e-2.

The Class II article[13] evaluated large numbers of newborns born to mothers taking enzyme-inducing AEDs compared to healthy controls. Upon evaluation of multiple risk factors for neonatal hemorrhage using logistic regression analysis, enzyme-inducing

AEDs did not emerge as significantly associated with neonatal hemorrhage (OR 1.1, 95% CI 0.3–4.6, $p = 0.8$). However, the high upper limit of the 95% CI indicates that the possibility of a substantial risk cannot be excluded. The majority of hemorrhages in AED-exposed newborns were accounted for by premature birth (<34 weeks). The Class III article[14] also showed no increased risk with AEDs, which were mostly enzyme-inducers (relative risk 0.51, 95% CI 0.21–1.24, $p = 0.14$). All newborns in both these studies received vitamin K 1 mg IM at birth, but the mothers received no prenatal vitamin K supplementation.

Conclusion. There is insufficient evidence to determine if the risk of neonatal hemorrhagic complications in the newborns of WWE taking AEDs is substantially increased (one inadequately sensitive Class II study).

Recommendation. Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is insufficient evidence to support or refute an increased risk of hemorrhagic complications in the newborns of WWE taking AEDs (Level U).

Does prenatal vitamin K supplementation reduce the risk of hemorrhagic complications in the newborns of WWE taking AEDs? No articles were found that provided higher than Class IV evidence.

Conclusion. Evidence is inadequate to determine if prenatal vitamin K supplementation in WWE reduces neonatal hemorrhagic complications.

Recommendation. There is insufficient evidence to support or refute a benefit of prenatal vitamin K supplementation for reducing the risk of hemorrhagic complications in the newborns of WWE (Level U).

Clinical context. Newborns exposed to enzyme-inducing AEDs in utero routinely receive vitamin K at delivery, as is the routine practice for all newborns.[15]

Do maternally ingested AEDs cross the placenta? Do maternally ingested AEDs penetrate into breast milk? Articles were included if the investigators measured AED levels in at least five mother-child pairs for evaluation of placental transfer and a minimum of five maternal serum-breast milk pairs. Each study's risk of bias was rated using the AAN prognostic classification of evidence scheme. The AED level in the mother's serum was the risk factor; the AED level in the neonate's serum was the outcome for the first question and the AED level in the breast milk was the outcome for the second question. Studies were downgraded because of inadequately described serum AED concentrations; nongeneralizable population; samples not obtained at uniform times, such as the maternal sample and the cord or milk sample obtained at differing times in the same

pair; or fewer than 80% of samples collected according to protocol.

There is no threshold level of passive exposure to AEDs that is established to impart a clinically important risk to the fetus or neonate. For the purpose of this parameter, the panel stipulated that an AED transfer rate of 0.6 (neonatal to maternal plasma concentration ratio or a milk to maternal concentration ratio) was potentially clinically important. Similarly, the panel stipulated that any trend of increasing plasma concentrations in the neonate by 25% over the evaluated period (generally 3 days up to 1 month) was clinically important.

The literature search identified 19 articles. Two articles were Class I, 16 were Class II, and one was Class III (see table e-3).

Placental transfer. One Class I study[16] and one Class II study[17] provided evidence that primidone (PRM) and phenobarbital (PB) significantly cross the placenta (cord:maternal concentration >0.6).

One Class I study[18] and two Class II studies[19,20] provided evidence that VPA significantly crosses the placenta.

At least two Class II studies per AED[19-24] provided evidence that the following AEDs significantly cross the placenta: phenytoin (PHT), carbamazepine (CBZ), and levetiracetam (LVT).

One Class II study for each of the following AEDs showed significant placental crossing: gabapentin (GBP),[25] lamotrigine (LTG),[26] oxcarbazepine (OXC),[27] and topiramate (TPM).[28]

One Class III study showed significant placental crossing for ethosuximide (ESM).[29]

Conclusions

- PB, PRM, PHT, CBZ, LVT, and VPA probably cross the placenta in potentially clinically important amounts (one Class I and supporting Class II studies or two or more Class II studies).
- GBP, LTG, OXC, and TPM possibly cross the placenta in potentially clinically important amounts (at least one Class II study for each).
- There are insufficient data to determine if ESM crosses the placenta in clinically important amounts (one Class III study showing significant penetration).

Recommendations. The fact that PB, PRM, PHT, CBZ, LVT, VPA, GBP, LTG, OXC, and TPM cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy (Level B for PB, PRM, PHT, CBZ, LVT, and VPA, and Level C for GBP, LTG, OXC, and TPM).

Breast milk penetration. One Class I study[16] and one Class II study[17]for PRM demonstrated significant penetration into breast milk.

Two Class II studies for LVT[23,24] demonstrated significant penetration into breast milk.

One Class II study for each of the following AEDs showed significant breast milk penetration: GBP,[25] LTG,[26] and TPM.[28]

One Class III study showed significant breast milk penetration for ESM.[29]

One Class I study[18] and a supporting Class II study[30] showed that VPA does not significantly penetrate into breast milk.

One Class I study[16] and one Class II study[17] provided evidence that PB does not significantly penetrate into breast milk.

Two Class II studies per AED provided evidence that CBZ[31,32] and PHT[33,34] do not significantly penetrate into breast milk.

The data were inadequate to show consistent evidence of accumulation of any AED in the newborn, including PB.

Conclusions

- PRM and LVT probably penetrate into breast milk in potentially clinically important amounts (one Class I study and a supporting Class II study or two Class II studies).
- GBP, LTG, and TPM possibly penetrate into breast milk in potentially clinically important amounts (one Class II study each).
- VPA, PB, PHT, and CBZ probably do not penetrate into breast milk in potentially clinically important amounts (one Class I study and a supporting Class II study or two Class II studies).
- There are insufficient data to determine if ESM penetrates into breast milk in clinically important amounts (one Class III study showing significant transfer).

Recommendations. VPA, PB, PHT, and CBZ may be considered as not transferring into breast milk to as great an extent as PRM, LVT, GBP, LTG, and TPM (Level B when compared to PRM and LVT and Level C when compared to GBP, LTG, and TPM).

Clinical context. Because of small sample size, there was no way to analyze the potential contribution of other clinical factors, such as AED polytherapy, on the passive transfer of AEDs to newborns of WWE.

Does indirect exposure to maternally ingested AEDs lead to symptomatic effects in the newborn? We defined pertinent symptomatic effects as those likely attributable to the AED (e.g., withdrawal, inconsolable fussiness, excessive sedation, lethargy). We searched for controlled studies comparing the frequency of such symptoms in the newborns of WWE on AEDs to WWE not on AEDs. No articles were identified.

Conclusion. There is no evidence to determine if indirect exposure to maternally ingested AEDs has symptomatic effects on the newborns of WWE.

Recommendation. None (Level U).

Clinical context. Certainly many of the AEDs cross through the placenta or into breast milk in measurable concentrations, with some meaningful differences in AEDs, particularly for breast milk transfer. The clinical consequences for the newborn of ingesting AEDs via breast milk remain sorely underexplored and will continue to produce anxiety in WWE bearing children and all who care for these clinical dyads.

For each of the AEDs, does pregnancy cause a change in the levels of the medication or clearance of the medication? Articles were included in the analysis if the investigators compared preconception and postpartum AED levels. Articles were classified according to the evidence for a prognostic article (appendix e-4B). Using this scheme, pregnancy was considered the predictor and a change in serum drug levels or drug clearance was considered the outcome.

Serum AED level assays were considered an objective outcome. However, other concerns about the assay's technical reliability and margin of error were considered as potential sources of bias and studies were downgraded accordingly. Trough sampling was not a requirement, but inconsistent times of sampling resulted in downgrading. Postpartum values >6 weeks were also accepted as an estimate for nonpregnant baseline. Changes in AED levels in WWE on polytherapy were accepted if it was clearly stated that other AED doses were kept the same. Articles that included WWE on polytherapy were downgraded.

No specific magnitude of change in AED level or clearance was required to be considered clinically important. However, the panel looked for evidence that an increase in seizure frequency was associated with a pregnancy-related decrease in AED levels.

Thirty-one relevant articles were identified by the literature search. Additionally, three articles published before 1985 were included in the analysis because they provided the only available information regarding some of the older AEDs. This was considered acceptable because the technology of AED level assays has been stable for decades. Three articles were classified as Class I, five were Class II, and 23 were Class III. For each AED, only the articles with the lowest risk of bias contributing to the conclusions are included in the evidence tables (see tables e-4–e-8).

Lamotrigine. One Class I study[35] showed that both LTG total and free clearance increased throughout pregnancy with a peak of 94% (total) and 89% (free) in the third trimester. Importantly, seizure frequency increased when the LTG level decreased to 65% of the

preconceptional individualized target LTG concentration. Two Class II studies[36,37] also showed an increase in the LTG clearance. One study[36] showed >65% increase in clearance between prepregnancy baseline and the second and third trimesters. The second study[37] showed that LTG clearance increased until 32 weeks of gestational age, with a peak of 230% above prepregnancy baseline. All three of these studies showed substantial variability among individuals in the magnitude of the enhanced LTG clearance.

Conclusion. Pregnancy probably causes an increase in the clearance and a decrease in the level of LTG during pregnancy. The decrease in LTG level is associated with an increase in seizure frequency (one Class I and two Class II studies).

Carbamazepine. One Class I study[38] of 35 women taking CBZ during pregnancy showed that total concentration of CBZ decreased by 9% in the second trimester and 12% in the third trimester compared to baseline. However, free CBZ levels did not change significantly during pregnancy compared to baseline. CBZ-epoxide concentrations, total and free, did not change. Two Class III studies[39,40] showed slightly increased clearance (10%–27.5%) during pregnancy, but one was confounded by findings only in women on polytherapy with enzyme-inducing AEDs.[40] One study[39] showed increased CBZ epoxide levels and increased epoxide: CBZ ratios during pregnancy.

Conclusion. Pregnancy probably causes a small decrease in concentration of CBZ (9% in second trimester and 12% in third trimester) (one Class I study).

Phenytoin. One Class I study[38] of 22 women taking PHT monotherapy showed that total PHT concentration decreased in all three trimesters from baseline (maximum of 61%). Free PHT concentrations decreased in the third trimester by 16%. The PHT free fraction increased in the second and third trimesters by a maximum of 40%. Plasma PHT clearance increased by up to 117% in all three trimesters compared to baseline. Free PHT clearance increased in the third trimester by 25%. Three Class II studies[e1-e3] also showed increased clearance and decreased levels during pregnancy.

Conclusion. Pregnancy probably causes an increase in the clearance and a decrease in the level of PHT during pregnancy (one Class I study).

Oxcarbazepine. Two Class III studies[e4,e5] observed a decrease in levels of the active metabolite of OXC, monohydroxy derivative (MHD). One study[e5] showed a mean decrease in MHD concentration of 61.5%, maximum in the second trimester. The other study[e4] showed that compared to before pregnancy, the mean dose-corrected concentration of MHD de-creased by 28% in the first trimester, 26% in the second trimester, and 36% in the third trimester.

Conclusion. Pregnancy possibly causes a decrease in the level of the active OXC metabolite, MHD (two Class III studies).

Levetiracetam. One Class II study[23] showed that concentrations of LVT decreased during pregnancy; maternal plasma concentrations during the third trimester decreased by 60% compared to prepregnancy baseline.

Conclusion. Pregnancy possibly causes a decrease in the level of LVT (one Class II study).

Phenobarbital, valproate, primidone, and ethosuximide. Sufficient monotherapy data are not available to provide evidence for a change in levels or clearance during pregnancy for PB, VPA, PRM, and ESM.

Conclusion. Evidence for a change in clearance or level of PB, VPA, PRM, and ESM during pregnancy is inadequate to reach a conclusion.

Recommendations

- Monitoring of LTG, CBZ, and PHT levels during pregnancy should be considered (Level B).
- Monitoring of LVT and OXC (as MHD) levels during pregnancy may be considered (Level C).
- There is insufficient evidence to support or refute a change in PB, VPA, PRM, or ESM levels related to pregnancy (Level U), and this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.

CLINICAL CONTEXT The studies reviewed provide some evidence supporting active monitoring of AED levels during pregnancy. This is especially true for LTG where changes in LTG levels were associated with increases in seizure frequency. It seems reasonable to individualize this monitoring for each patient with the aim of maintaining a level near the preconceptional level, presumably at which the woman with epilepsy was doing well with seizure control. However, the studies reviewed fall short of determining that adoption of an active AED monitoring program would result in improved seizure control during pregnancy.

Unfortunately, the studies reviewed provided no clear data on the timing of the return to the prepregnancy pharmacokinetic state after pregnancy. One study[35] demonstrated that following an empiric postpartum taper schedule of LTG reduced the occurrence of postpartum toxicity, but more systematic information is needed regarding the pharmacokinetic alterations in AED metabolism postpartum for all AEDs in order to determine the management of AED dosing in the postpartum period.

RECOMMENDATIONS FOR FUTURE RE-SEARCH The issue of whether preconceptional folic

acid supplementation for WWE, particularly at high doses, provides additional benefit in preventing MCMs needs to be clarified. Similarly, the risk of hemorrhagic disease of the newborn in neonates born to WWE taking AEDs and whether late-pregnancy vitamin K supplementation could be beneficial need to be determined. Studies of some commonly used AEDs, such as zonisamide or TPM, were so limited that no recommendations could be made regarding these specific medications.

Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms; more defined study on acute and prolonged outcomes in exposed neonates needs to be performed. This is particularly true for more subtle side effects, such as cognition and general healthy neonatal development. Information about how AED levels change during pregnancy based on individual metabolic capacity, as well as neonatal metabolism of AEDs consumed through breast milk, is needed in order to guide dosing and clinical monitoring of both mother and infant.

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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. 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, NINDS, NIMH, CDC, and Emory University Research Council. Dr. Koppel reports no disclosures. Dr. Hovinga estimates less than 10% of his clinical effort is spent on pharmacology consults. Dr. Gidal has served on the scientific advisory board for GlaxoSmithKline, UCB Pharma, and Abbott Labs and served as an editor for *Epilepsy & Behavior*, *The Annals of Pharmacotherapy*, and *Pharmacist's Letter*. Dr. Gidal has received research support from UCB Pharma. Dr. Meador serves as a journal editor for *Neurology, Journal of Clinical Neurophysiology, Cognitive and Behavioral Neurology, Epilepsy & Behavior, Epilepsy Currents*, and Epilepsy.com. He has received research funding from NIH/NINDS, GlaxoSmithKline, Eisai, Marius, Myriad, Neuropace, SAM Technology, and UCB Pharma. Dr. Meador estimates that 30–40% of his clinical effort is spent on EEGs and the clinical care of patients with epilepsy. 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. 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, and Hotchkiss Neurological Institute, and has given expert testimony in his role as an FAA consultant. Dr. Thurman is an employee of the CDC. 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 receives 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. 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. Wiebe serves on the editorial board of *Neurology, Epilepsia, Epilepsy & Behavior*, and *Canadian Journal of Neurological Sciences*. Dr. Wilner has served on the scientific advisory board of and received funding for travel from GlaxoSmithKline. 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McNeil, and Eisai. Dr. Vazquez has served on a speakers' bureau for Eisai, GSK, Ortho McNeil, UCB, and Novartis. Dr. Holmes receives research support from Abbott Labs, 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. Ms. Shafer has served on the scientific advisory board for GlaxoSmithKline, has received funding for travel from the Epilepsy Therapy Project, and acts as a reviewer for *Epilepsy & Behavior* and *Epilepsia*. She has received honoraria from Medscape, American Epilepsy Society, and Cyberonics Nursing Advisory Board. Ms. Shafer is on the speakers' bureau of the Epilepsy Foundation of Massachusetts and Rhode Island, acts as a consultant to the Epilepsy Therapy Project, and is a contributing writer at epilepsy.com. Ms. Le Guen reports no disclosures.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. 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 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.

REFERENCES

1. 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. July 1st resident population by state, county, age, sex, bridged-race, and Hispanic origin on CDC WONDER On-line Database. Available at: http://wonder.cdc.gov. Accessed June 2008.
2. Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the "common" neurologic disorders? Neurology 2007;68:326–337.
3. Yerby MS. Quality of life, epilepsy advances, and the evolving role of anticonvulsants in women with epilepsy. Neurology 2000;55:S21–31.
4. Harden CL, Hopp J, Ting TY, et al. Practice Parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the Ameri-
can Academy of Neurology and American Epilepsy Society. Neurology 2009;73:126–132.
5. Holmes LB, Harvey EA, Coull BA, et al. The teratogenicity of anticonvulsant drugs. N Engl J Med 2001;344:1132–1138.
6. Betts T, Fox C. Proactive preconception counseling for women with epilepsy: is it effective? Seizure 1999;8:322–327.
7. Kaaja E, Kaaja R, Hiilesmaa V. Major malformations in offspring of women with epilepsy. Neurology 2003;60:575–579.
8. Vajda FJ, O'Brien TJ, Hitchcock A, et al. The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. J Clin Neurosci 2003;10:543–549.
9. Vajda FJ, O'Brien TJ, Hitchcock A, et al. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. J Clin Neurosci 2004;11:854–858.
10. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Homes LB. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology 2005;64:961–965.
11. Czeizel AE, Dobó M, Vargha P. Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. Birth Defects Res A Clin Mol Teratol 2004;70:853–861.
12. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. Morb Mortal Wkly Rep 1992; September 11/41(RR-14):001.
13. Kaaja E, Kaaja R, Matila R, Hiilesmaa V. Enzyme-inducing antiepileptic drugs in pregnancy and the risk of bleeding in the neonate. Neurology 2002;58:549–553.
14. Choulika S, Grabowski, Holmes LB. Is antenatal vitamin K prophylaxis needed for pregnant women taking anticonvulsants? Am J Obstet Gynecol 2004;190:882–883.
15. American Academy of Pediatrics Vitamin K Ad Hoc Task Force. Controversies concerning vitamin K and the newborn. Pediatrics 1993;91:1001–1003.
16. Kuhnz W, Koch S, Helge H, Nau H. Primidone and phenobarbital during lactation period in epileptic women: total and free drug levels in the nursed infants and their effects on neonatal behavior. Dev Pharmacol Ther 1988;11:147–154.
17. Nau H, Rating D, Häuser I, Jäger E, Koch S, Helge H. Placental transfer and pharmacokinetics of primidone and its metabolites phenobarbital, PEMA and hydroxyphenobarbital in neonates and infants of epileptic mothers. Eur J Clin Pharmacol 1980;18:31–42.
18. Nau H, Rating D, Koch S, Hauser I, Helge H. Valproic acid and its metabolites: Placental transfer, neonatal pharmacokinetics, transfer via mother's milk and clinical status in neonates of epileptic mothers. J Pharmacol Exp Ther 1981;219:768–777.
19. Takeda A, Okada H, Tanaka H, et al. Protein binding of four antiepileptic drugs in maternal and umbilical cord serum. Epilepsy Res 1992;13:147–151.
20. Ishizaki T, Yokochi K, Chiba K, et al. Placental transfer of anticonvulsants (phenobarbital, phenytoin, valproic acid) and elimination from neonates. Pediatr Pharmacol 1981;1:291–303.

21. Gomita Y, Furuno K, Akaki Y, et al. Phenobarbital in sera of epileptic mothers and their infants. Am J Ther 1995;2:968–971.

22. Yerby MS, Friel PN, McCormick K, et al. Pharmacokinetics of anticonvulsants in pregnancy: alterations in plasma protein binding. Epilepsy Res 1990;5:223–228.

23. Tomson T, Palm R, Källén K, et al. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. Epilepsia 2007;48:1111–1116.

24. Johannessen SI, Helde G, Brodtkorb E. Levetiracetam concentrations in serum in breast milk at birth and during lactation. Epilepsia 2005;46:775–777.

25. Ohman I, Vitols S, Tomson T. Pharmacokinetics of gabapentin during delivery, in the neonatal period and lactation: does fetal accumulation occur during pregnancy? Epilepsia 2005;46:1621–1624.

26. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. Epilepsy 2000;41:709–713.

27. Myllynen P, Pienimaki P, Jouppila P, et al. Transplacental passage of oxcarbazepine and its metabolites in vivo. Epilepsia 2001;42:1482–1485.

28. Ohman I, Vitols S, Luef G, et al. Topiramate kinetics during delivery, lactation, and in the neonate: Preliminary observations. Epilepsia 2002;43:1157–1160.

29. Kuhnz W, Koch S, Jakob S, Hartmann A, Helge H, Nau H. Ethosuximide in epileptic women during pregnancy and lactation period: Placental transfer, serum concentrations in nursed infants and clinical status. Br J Clin Pharmacol 1984;18:671–677.

30. Nau H, Helge H, Luck W. Valproic acid in the perinatal period: decreased maternal serum protein binding results in fetal accumulation and neonatal displacement of the drug and some metabolites. J Pediatr 1984;104:627–634.

31. Froescher W, Eichelbaum M, Niesen M, et al. Carbamazepine levels in breast milk. Ther Drug Monit 1984;6:266–271.

32. Kuhnz W, Jager-Roman E, Rating D, et al. Carbamazepine and carbamazepine-10, 11-epoxide during pregnancy and postnatal period in epileptic mothers and their nursed infants: clinical and pharmacokinetic effects. Pediatr Pharmacol 1983;3:199–208.

33. Mirkin BL. Diphenylhydantoin: placental transfer, fetal localization, neonatal metabolism and possible teratogenic effects. J Pediatr 1971;78:329–337.

34. Steen B, Rane A, Lonnerholm G, et al. Phenytoin excretion in human breast milk and plasma levels in nursed infant. Ther Drug Monit 1982;4:331–334.

35. Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology 2008;70:2130–2136.

36. Tran TA, Leppik IE, Blesi K, et al. Lamotrigine clearance during pregnancy. Neurology 2002;59:251–255.

37. Pennell P, Newport DJ, Stow ZN, et al. The impact of pregnancy and childbirth on the metabolism of lamotrigine. Neurology 2004;62:292–295.

38. Tomson T, Lindbom U, Ekqvist B, et al. Epilepsy and pregnancy: a prospective study of seizures control in relation to free and total plasma concentrations of carbamazepine and phenytoin. Epilepsia 1994;35:122–130.

39. Battino D, Binelli S, Bossi L, et al. Plasma concentrations of carbamazepine and carbamazepine 10, 11-epoxide during pregnancy and after delivery. Clin Pharmacokinet 1985;10:279–284.

40. Bernus I, Hooper WD, Dickinson RG, et al. Metabolism of carbamazepine and co-administered anticonvulsants during pregnancy. Epilepsy Res 1995;21:65–75.

The Child Neurology Society has endorsed the following guidelines:

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

- Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes

- Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels, and breastfeeding