MANAGEMENT ISSUES FOR WOMEN WITH EPILEPSY—FOCUS ON PREGNANCY VITAMIN K, FOLIC ACID, BLOOD LEVELS, AND BREASTFEEDING

This is a summary of the American Academy of Neurology (AAN) guideline regarding management and care of women with epilepsy (WWE) during pregnancy. Recommendations are presented for prenatal 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.

Please refer to the full guideline at www.aan.com for more information.

RISKS TO NEWBORNS/NEONATES

Does preconceptional folic acid supplementation reduce the risk of birth defects in neonates of WWE taking AEDs?	
Weak evidence	Preconceptional folic acid supplementation in WWE may be considered to reduce the risk of major congenital malformations (MCMs) (**Level C**†).
Clinical context*	Folic acid supplementation is generally recommended to reduce the risk of MCMs during pregnancy, 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, all women of childbearing potential, with or without epilepsy, should be encouraged to take at least 0.4 mg of folic acid daily prior to conception and during pregnancy. There was insufficient published information to address the dosing of folic acid.
What is the risk of hemorrhagic disease in neonates born to WWE taking AEDs?	
Insufficient evidence	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?	
Insufficient evidence	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.
Do maternally ingested AEDs cross the placenta or penetrate into breast milk?	
Good evidence	The fact that phenobarbital (PB), primidone (PRM), phenytoin (PHT), carbamazepine (CBZ), levetiracetam (LVT), and valproate (VPA) cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy (**Level B**).
	VPA, PB, PHT, and CBZ may be considered as not transferring into breast milk to as great an extent as PRM and LVT **(Level B**).
Weak evidence	The fact that gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC), and topiramate (TPM) cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy (**Level C**).
	VPA, PB, PHT, and CBZ may be considered as not transferring into breast milk to as great an extent as GBP, LTG, and TPM (**Level C**).
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?	
Insufficient evidence	No recommendation has been made (**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. The clinical consequences for the newborn of ingesting AEDs via breast milk remain sorely underexplored.

CHANGE IN AED LEVELS	
For each of the AEDs, does pregnancy cause a change in the levels of the medication or clearance of the medication?	
Good evidence	Monitoring of LTG, CBZ, and PHT levels during pregnancy should be considered (**Level B**).
Weak evidence	Monitoring of LVT and OXC (as a monohydroxy derivative [MHD]) levels during pregnancy may be considered (**Level C**).
Insufficient evidence	There is insufficient evidence to support or refute a change in PB, VPA, PRM, or ethosuximide (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, particularly of LTG, as changes in LTG levels were associated with increased 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.

**Clinical context slightly abridged. See the published guideline for the complete text.*

This guideline summary is evidence-based. The AAN uses the following definitions for the level of recommendations and classification of evidence for therapeutic intervention and prognosis.

†**Classification of Recommendations: A** = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)** **B** = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.) **C** = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.) **U** = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

**In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

Classification of Evidence for Studies of Therapeutic Intervention: Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required: a. concealed allocation, b. primary outcome(s) clearly defined, c. exclusion/inclusion criteria clearly defined, d. adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias, e. for non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required***: 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority. 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective). 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment. 4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers. **Class II** = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. **Class III** = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**** **Class IV** = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

***Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

****Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Classification of Evidence for Rating of a Prognostic Article: Class I = A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy. **Class II** = A case control study of a broad spectrum of persons with the condition compared to a broad spectrum of controls or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy. **Class III** = A case control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy. **Class IV** = Studies not meeting Class I, II, or III criteria including consensus, expert opinion or a case report.

This is an educational service of the American Academy of Neurology. It is designed to provide members with evidence-based guideline recommendations to assist the decision making in patient care. It is based on an assessment of current scientific and clinical information and is not 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, and are based on the circumstances involved. Physicians are encouraged to review carefully the full AAN guidelines so they understand all recommendations associated with care of their patients.

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