

# WOMEN WITH EPILEPSY: DRUG RISKS AND SAFETY DURING PREGNANCY

This fact sheet may help you understand which drugs are safest for treating epilepsy during pregnancy. It also gives information on how safe pregnancy is for you now or in the future.

Neurologists from the American Academy of Neurology are doctors who identify and treat diseases of the brain and nervous system. The following evidence-based information\* is provided by experts who carefully reviewed all available scientific studies concerning women with epilepsy who are pregnant or plan to become pregnant.

If you have epilepsy, it is important to know the risks of taking antiepileptic drugs (AEDs) during pregnancy—especially valproate (VPA). But you should also know that pregnancy is relatively safe for you and your baby.

Most of the evidence for the risks discussed in this fact sheet relates to VPA use. The risks of taking other AEDs are not discussed here.

## I have epilepsy and plan to become pregnant. Will taking an AED during pregnancy put me at risk for a difficult pregnancy?

Taking an AED during pregnancy is not likely to lead to a difficult pregnancy. There is good evidence that taking AEDs while you are pregnant will not put you at an especially high risk of late-pregnancy bleeding. There is weak evidence that AED use raises your risk of Cesarean section, but good evidence shows the risk is not very high. Good evidence also shows that you will not be at very high risk of early contractions or early labor and delivery. There is not enough evidence to know if taking AEDs during pregnancy raises your odds of having pregnancy-related high blood pressure.

## If I take VPA while I'm pregnant, will my baby be at risk for health problems?

Taking VPA during the first trimester of pregnancy is related to three major birth defects: neural tube defects, facial clefts, and hypospadias. This last defect occurs in boys. It causes the urinary opening to form below the tip or on the side of the penis. There is good evidence that avoiding VPA use in the first trimester lowers the risk of neural tube defects and facial clefts. The evidence is weak that avoiding VPA use in the first trimester lowers the risk of hypospadias. VPA use can also lead to poorer thinking ability. There is good evidence for avoiding VPA use during pregnancy to lower this risk.

## How risky is taking VPA during pregnancy compared to taking other AEDs?

Some studies compared the risks of using VPA during pregnancy to the risks of using certain other AEDs. The

evidence points to avoiding VPA use in the first trimester to lower the risk of birth defects. It also suggests avoiding VPA use throughout pregnancy to decrease the risk of poorer thinking ability.

## How risky is taking more than one AED at a time during pregnancy?

Good evidence shows that women with epilepsy should consider taking one AED instead of more than one during their first trimester to lower the risk of major birth defects. If you cannot avoid taking more than one AED, be aware that there is some evidence for avoiding VPA in particular as part of your therapy during your first trimester. This is because multidrug therapy with VPA is related to birth defects.

In addition, there is good evidence for taking one AED instead of more than one during pregnancy to decrease the risk of poorer thinking ability.

## How is my baby exposed to AEDs during pregnancy? Will my baby be exposed to my AED during breastfeeding?

Several AEDs are able to pass through the umbilical cord from the pregnant woman to her fetus. There is no evidence to know if this affects the baby's health. There is good evidence for considering this information when deciding whether to take VPA during pregnancy. The evidence varies for the risks of other drugs. There is some evidence that VPA might pass through breastfeeding to your baby in smaller amounts than some other AEDs.

## **I have epilepsy and plan to become pregnant. What is the risk that my baby will die because of my epilepsy? Does taking an AED during pregnancy change the risk?**

There is good evidence that the babies of women with epilepsy are not at any higher risk of dying in the first month of life than the babies of women without epilepsy. It is not known if AED use during pregnancy changes the risk level. There is not enough evidence to show whether taking AEDs during pregnancy raises the chance of miscarriage.

## **What can I do to lower the risks to my baby's health?**

It may be possible to lower your baby's risk of birth defects. Doctors typically recommend that all women who are planning pregnancy take folic acid (vitamin B9) to lower the risk of birth defects. There is weak evidence that taking folic acid before pregnancy will help women with epilepsy in particular. Keep in mind that taking folic acid before you become pregnant will not harm your baby and might help.

## **I have epilepsy and plan to become pregnant. What can I do to lower my chance of health problems during my pregnancy?**

If you have epilepsy and smoke cigarettes, you may want to avoid smoking while you are pregnant. Weak evidence shows that smoking during pregnancy may lead to an especially high risk of early contractions and early labor and delivery—even if you are not taking AEDs while pregnant. Talk with your doctor about what to do if you smoke and are pregnant or are planning pregnancy. Health habits other than smoking were not covered in these studies.

## **How do I know if I should stay on medication when I'm pregnant?**

AED use during pregnancy—especially VPA use—has some risks. But there are many good reasons to consider staying on AEDs during pregnancy. Seizure can be dangerous to both you and your fetus. So working toward being free of seizure is important. Good evidence shows that women who are seizure free for nine months or more before pregnancy will likely remain seizure free throughout pregnancy. Also, AED levels can drop during pregnancy, so be sure to work closely with your doctor to maintain the right AED level for you.

There is not enough evidence to know if pregnancy changes your odds of other epilepsy-related problems like status epilepticus or a higher seizure rate.

It is important to work with your doctor when deciding if you will stay on AEDs during pregnancy. Keep in mind that some AEDs are safer than others. Stopping AED use—whether before or during pregnancy—might not be best for you. Also, if you are pregnant and taking an AED, switching to another AED now might bring on other health problems. Whatever your situation, talk to your doctor about making the right choice for you.

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.

\*After the experts review all of the published research studies, they describe the strength of the evidence supporting each recommendation:

*Strong* evidence = more than one high-quality scientific study

*Good* evidence = at least one high-quality scientific study or two or more studies of a lesser quality

*Weak* evidence = the studies, while supportive, are weak in design or strength of the findings

*Not enough* evidence = either different studies have come to conflicting results or there are no studies of reasonable quality

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## 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](http://www.aan.com) for more information.*

RISKS TO NEWBORNS/NEONATES	
<b>Does preconceptional folic acid supplementation reduce the risk of birth defects in neonates of WWE taking AEDs?</b>	
<b>Weak evidence</b>	Preconceptional folic acid supplementation in WWE may be considered to reduce the risk of major congenital malformations (MCMs) ( <b>Level C<sup>†</sup></b> ).
<b>Clinical context*</b>	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.
<b>What is the risk of hemorrhagic disease in neonates born to WWE taking AEDs?</b>	
<b>Insufficient evidence</b>	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 ( <b>Level U</b> ).
<b>Does prenatal vitamin K supplementation reduce the risk of hemorrhagic complications in the newborns of WWE taking AEDs?</b>	
<b>Insufficient evidence</b>	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 ( <b>Level U</b> ).
<b>Clinical context</b>	Newborns exposed to enzyme-inducing AEDs in utero routinely receive vitamin K at delivery, as is the routine practice for all newborns.
<b>Do maternally ingested AEDs cross the placenta or penetrate into breast milk?</b>	
<b>Good evidence</b>	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 ( <b>Level B</b> ).
	VPA, PB, PHT, and CBZ may be considered as not transferring into breast milk to as great an extent as PRM and LVT ( <b>Level B</b> ).
<b>Weak evidence</b>	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 ( <b>Level C</b> ).
	VPA, PB, PHT, and CBZ may be considered as not transferring into breast milk to as great an extent as GBP, LTG, and TPM ( <b>Level C</b> ).
<b>Clinical context</b>	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.
<b>Does indirect exposure to maternally ingested AEDs lead to symptomatic effects in the newborn?</b>	
<b>Insufficient evidence</b>	No recommendation has been made ( <b>Level U</b> ).
<b>Clinical context</b>	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?**

<b>Good evidence</b>	Monitoring of LTG, CBZ, and PHT levels during pregnancy should be considered ( <b>Level B</b> ).
<b>Weak evidence</b>	Monitoring of LVT and OXC (as a monohydroxy derivative [MHD]) levels during pregnancy may be considered ( <b>Level C</b> ).
<b>Insufficient evidence</b>	There is insufficient evidence to support or refute a change in PB, VPA, PRM, or ethosuximide (ESM) levels related to pregnancy ( <b>Level U</b> ), and this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
<b>Clinical context</b>	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<sup>\*\*\*</sup>: 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.<sup>\*\*\*\*</sup> **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.

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## MANAGEMENT ISSUES FOR WOMEN WITH EPILEPSY— FOCUS ON PREGNANCY OBSTETRICAL COMPLICATIONS AND CHANGE IN SEIZURE FREQUENCY

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 obstetric or other health complications, change in seizure frequency, risk of status epilepticus, and rate of continued seizure freedom during pregnancy.

*Please refer to the full guideline at [www.aan.com](http://www.aan.com) for more information.*

### OBSTETRICAL COMPLICATIONS

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

<b>Good evidence</b>	Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is probably no substantially increased risk (greater than 2 times expected) of Cesarean delivery for WWE taking antiepileptic drugs (AEDs) ( <b>Level B<sup>+</sup></b> ).
	Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is probably no substantially increased risk (greater than 2 times expected) of late pregnancy bleeding for WWE taking AEDs ( <b>Level B</b> ).
	Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is probably no moderately increased risk (greater than 1.5 times expected) of premature contractions or premature labor and delivery for WWE taking AEDs ( <b>Level B</b> ).
<b>Weak evidence</b>	Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is possibly a moderately increased risk (up to 1.5 times expected) of Cesarean delivery for WWE taking AEDs ( <b>Level C</b> ).
	Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is possibly a substantially increased risk of premature contractions or premature labor and delivery during pregnancy for WWE who smoke ( <b>Level C</b> ).
<b>Insufficient evidence</b>	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 pre-eclampsia, pregnancy-related hypertension, or spontaneous abortion ( <b>Level U</b> ).

### EPILEPSY-RELATED COMPLICATIONS

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

<b>Good evidence</b>	Counseling of WWE who are pregnant or are contemplating pregnancy should reflect 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 ( <b>Level B</b> ).
<b>Insufficient evidence</b>	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 a change in seizure frequency or status epilepticus ( <b>Level U</b> ).

### CLINICAL CONTEXT\*

There was no conclusive evidence of an increased risk of many obstetrical complications often 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.

Further, the findings do not suggest high rates of status epilepticus, increased seizure rate, or increased risk of seizure relapse during pregnancy for WWE who are seizure free. The available data indicate that seizure-free WWE will remain seizure free during pregnancy, which is another reason to strive for seizure freedom in WWE planning pregnancy.

*\*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 prognosis and screening.

**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 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.

**Classification of Evidence for Rating of a Screening Article:** **Class I** = A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations. **Class II** = A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations. **Class III** = A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician. **Class IV** = Studies not meeting Class I, II, or III criteria including consensus, expert opinion or a case report.

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## MANAGEMENT ISSUES FOR WOMEN WITH EPILEPSY— FOCUS ON PREGNANCY TERATOGENESIS AND PERINATAL OUTCOMES

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 risk of major congenital malformations (MCMs) associated with intrauterine exposure to antiepileptic drugs (AEDs) in neonates born to WWE; risk of adverse long-term cognitive outcomes in children born to WWE; and risk of death, low birth weight, and low Apgar scores in neonates born to WWE.

**Please refer to the full guideline at [www.aan.com](http://www.aan.com) for more information.**

MAJOR CONGENITAL MALFORMATIONS	
<b>Do AEDs taken during the first trimester of pregnancy increase the risk of MCMs in the offspring of WWE compared to the offspring of WWE not on AEDs?</b>	
<b>Good evidence</b>	If possible, avoidance of the use of valproate (VPA) as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of MCMs ( <b>Level B<sup>+</sup></b> ).
<b>Weak evidence</b>	If possible, avoidance of the use of VPA monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs ( <b>Level C</b> ).
<b>Insufficient evidence</b>	Although there is evidence that AEDs taken during the first trimester probably increase the risk of MCMs in the offspring of WWE, it cannot be determined if the increased risk is imparted from all AEDs or from only one or some AEDs. Therefore, no recommendation is made from this conclusion ( <b>Level U</b> ).
<b>Is exposure to a specific AED during the first trimester of pregnancy associated with an increased risk of MCMs compared to exposure to other AEDs?</b>	
<b>Strong evidence</b>	To reduce the risk of MCMs, the use of VPA during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine (CBZ) ( <b>Level A</b> ).
<b>Good evidence</b>	To reduce the risk of MCMs, avoidance of the use of polytherapy with VPA during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without VPA ( <b>Level B</b> ).
<b>Weak evidence</b>	To reduce the risk of MCMs, avoidance of the use of VPA during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin (PHT) or lamotrigine (LTG) ( <b>Level C</b> ).
<b>Is the risk of MCMs greater for AED polytherapy compared to AED monotherapy when taken during the first trimester of pregnancy?</b>	
<b>Good evidence</b>	To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered ( <b>Level B</b> ).
<b>Is there a relationship between AED dose and the risk of MCMs in the offspring of WWE?</b>	
<b>Good evidence</b>	Limiting the dosage of VPA or LTG during the first trimester, if possible, should be considered to lessen the risk of MCMs ( <b>Level B</b> ).
<b>Are there specific MCMs associated with specific AEDs?</b>	
<b>Good evidence</b>	Avoidance of the use of VPA, if possible, should be considered to reduce the risk of neural tube defects and facial clefts ( <b>Level B</b> ).
<b>Weak evidence</b>	Avoidance of the use of VPA, if possible, may be considered to reduce the risk of hypospadias ( <b>Level C</b> ).
	Avoidance of PHT, CBZ, and phenobarbital (PB), if possible, may be considered to reduce the risk of specific MCMs: cleft palate for PHT use, posterior cleft palate for CBZ use, and cardiac malformations for PB use ( <b>Level C</b> ).

COGNITIVE TERATOGENESIS	
<b>Is cognitive outcome reduced in children of WWE who are not exposed to AEDs in utero?</b>	
<b>Good evidence</b>	Counseling of WWE who are contemplating pregnancy should reflect that there is probably no increased risk of reduced cognition in the offspring of WWE not taking AEDs ( <b>Level B<sup>++</sup></b> ).
<b>Is cognition reduced in children of WWE exposed to AEDs in utero?</b>	
<b>Good evidence</b>	Avoiding VPA in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes ( <b>Level B</b> ).
<b>Weak evidence</b>	Avoiding PHT in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes ( <b>Level C</b> ).
	Avoiding PB in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes ( <b>Level C</b> ).

<b>Does AED polytherapy exposure during pregnancy pose an increased risk for poor cognitive outcome compared to monotherapy?</b>	
<b>Good evidence</b>	Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy, to reduce the risk of poor cognitive outcomes ( <b>Level B</b> ).
<b>Is exposure to a specific AED in utero associated with poor cognitive outcomes compared to other AEDs?</b>	
<b>Good evidence</b>	For WWE who are pregnant, avoidance of VPA, if possible, should be considered, compared to CBZ to reduce the risk of poor cognitive outcomes ( <b>Level B</b> ).
<b>Weak evidence</b>	For WWE who are pregnant, avoidance of VPA, if possible, may be considered compared to PHT to reduce the risk of poor cognitive outcomes ( <b>Level C</b> ).

## ADVERSE PERINATAL OUTCOMES

<b>Is there an increased risk of small for gestational age (SGA) outcomes in neonates born to WWE?</b>	
<b>Good evidence</b>	Pregnancy risk stratification should reflect that the offspring of WWE taking AEDs during pregnancy probably have an increased risk of SGA. Further, AED use in WWE during pregnancy should be considered in the differential diagnosis of SGA in their offspring ( <b>Level B<sup>††</sup></b> ).
<b>Is there an increased risk of perinatal death in neonates born to WWE?</b>	
<b>Good evidence</b>	Pregnancy risk stratification should reflect that neonates born to WWE probably do not have a substantially increased risk of perinatal death ( <b>Level B</b> ).
<b>Are Apgar scores lower in neonates born to WWE?</b>	
<b>Weak evidence</b>	Pregnancy risk stratification should reflect that the offspring of WWE taking AEDs during pregnancy possibly have an increased risk of 1-minute Apgar scores of <7. Further, AED use in WWE during pregnancy may be considered in the differential diagnosis of a 1-minute Apgar score of <7 in their offspring ( <b>Level C</b> ).

## CLINICAL CONTEXT\*

AEDs can prevent seizures during pregnancy, which by extension protects the fetus. For most WWE, discontinuing AEDs is not a reasonable or safe option; it may expose the mother and fetus to physical injury from seizure-related accidents.

It seems reasonable to switch WWE of childbearing potential to a less teratogenic regimen when possible. VPA, although effective, emerges as the AED with the greatest number of data associating it with risk from in-utero exposure. It seems that changing from VPA to another AED should be done well before pregnancy. Changing to another AED during pregnancy poses risk of allergy, other serious adverse reactions, and polytherapy exposure. Changing from VPA several weeks into gestation will not avoid the risk of MCMs, as MCMs develop very early in pregnancy.

The studies of many AEDs were too small to make conclusions, and the teratogenicity of these drugs is unknown.

MCMs seen more frequently with VPA, such as neural tube defects, can also be present with exposure to other AEDs, demonstrating that this is not an AED-specific MCM. Like other teratogens, AEDs produce a pattern of MCMs with overlap amongst the individual AEDs.

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

<sup>†</sup>Recommendations for causality: **A** = risk factor is a highly probable contributor; **B** = risk factor is a probable contributor; **C** = risk factor is a possible contributor; **U** = causal relationship unproven/unsupported.

<sup>††</sup>Recommendations for prognosis: **A** = established as effective, ineffective, or harmful; **B** = probably effective, ineffective, or harmful; **C** = possibly effective, ineffective, or harmful; **U** = data inadequate or conflicting.

Please see the full-text guideline for the AAN's definitions of the levels of recommendations and classifications of evidence.

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