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 for more information.

MAJOR CONGENITAL MALFORMATIONS

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?	
Good evidence	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 (**Level B**†).
Weak evidence	If possible, avoidance of the use of VPA monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs (**Level C**).
Insufficient evidence	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 (**Level U**).
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?	
Strong evidence	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) (**Level A**).
Good evidence	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 (**Level B**).
Weak evidence	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) (**Level C**).
Is the risk of MCMs greater for AED polytherapy compared to AED monotherapy when taken during the first trimester of pregnancy?	
Good evidence	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 (**Level B**).
Is there a relationship between AED dose and the risk of MCMs in the offspring of WWE?	
Good evidence	Limiting the dosage of VPA or LTG during the first trimester, if possible, should be considered to lessen the risk of MCMs (**Level B**).
Are there specific MCMs associated with specific AEDs?	
Good evidence	Avoidance of the use of VPA, if possible, should be considered to reduce the risk of neural tube defects and facial clefts (**Level B**).
Weak evidence	Avoidance of the use of VPA, if possible, may be considered to reduce the risk of hypospadias (**Level C**).
	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 (**Level C**).

COGNITIVE TERATOGENESIS

Is cognitive outcome reduced in children of WWE who are not exposed to AEDs in utero?	
Good evidence	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 (**Level B**††).
Is cognition reduced in children of WWE exposed to AEDs in utero?	
Good evidence	CBZ exposure probably does not produce cognitive impairment in offspring of WWE (**Level B**).
	Avoiding VPA in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes (**Level B**).
Weak evidence	Avoiding PHT in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (**Level C**).
	Avoiding PB in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (**Level C**).

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

ADVERSE PERINATAL OUTCOMES

Is there an increased risk of small for gestational age (SGA) outcomes in neonates born to WWE?	
Good evidence	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 (**Level B**[††]).
Is there an increased risk of perinatal death in neonates born to WWE?	
Good evidence	Pregnancy risk stratification should reflect that neonates born to WWE probably do not have a substantially increased risk of perinatal death (**Level B**).
Are Apgar scores lower in neonates born to WWE?	
Weak evidence	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 (**Level C**).

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.*

[†]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.

[††]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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