AAN Summary of Practice Guideline for **Clinicians**

Teratogenesis, perinatal, and neurodevelopmental outcomes after in utero exposure to antiseizure medication: Practice guideline from the AAN, AES, and SMFM

This is a summary of the American Academy of Neurology (AAN), American Epilepsy Society (AES), and Society for Maternal-Fetal Medicine (SMFM) guideline, "Teratogenesis, perinatal, and neurodevelopmental outcomes after in utero exposure to antiseizure medication," which was published in *Neurology*® online on May 15, 2024.

Please refer to the full guideline at AAN.com/guidelines for more information, including the full systematic review of the evidence as well as descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

General

Recommendation 1

Rationale

The overarching goals of care for people with epilepsy of childbearing potential (PWECP) are to optimize health outcomes both for individuals and their future offspring. In many cases, in utero antiseizure medication (ASM) exposure may be associated with increased risks to the fetus. There are also risks associated with discontinuing or changing ASMs in PWECP.[1,2,3,4] A shared decision-making process leads to more informed choices, a better understanding of available options, a more accurate risk perception, and improved decision quality grounded in individual values.[5] This decision-making process may take into account an individual's plans for pregnancy. However, according to the Epilepsy Birth Control Registry of 1,114 PWECP in the United States, more than 65% of pregnancies among PWECP are unintended.[6,7] The ASM regimen employed for a PWECP when pregnancy is not planned is thus very often the regimen used at the time of conception.

Level	Recommendation
Level B	1A. Clinicians should engage in joint decision-making with PWECP, taking individual preferences into account when selecting ASMs and monitoring their dosing.
Level B	1B. When treating PWECP, clinicians should recommend ASMs and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally (e.g., at the time of starting an ASM in a person post-menarche).

Recommendation 2

Rationale

The odds of mortality during pregnancy are 5–12 times greater among PWECP as compared to pregnant people without epilepsy, according to an analysis of a Danish cohort of more than 2 million pregnancies and a US cohort of more than 20 million participants.[8,9] Among 202 pregnancy-related deaths in the UK from 2013–2015, the majority of the 13 epilepsy-related deaths were from sudden unexpected death in epilepsy (SUDEP). All participants with prepregnancy data had uncontrolled seizures. Five of the participants who died had stopped taking their ASMs during pregnancy.[10]

In an analysis of the EURAP study including 1,956 pregnancies among 1,882 participants, there was no statistical association between seizures during pregnancy and spontaneous abortion or stillbirth. However, the 1 stillbirth that occurred soon after a seizure was an episode of convulsive status epilepticus. The frequency of generalized tonic-clonic seizures or focal to bilateral tonic-clonic seizures may also be a risk factor for lower IQ in children born to PWECP.[1]

Valproic acid is one of the most effective ASMs at obtaining adequate seizure control among people with idiopathic generalized epilepsy.[3,4] An analysis of the EURAP cohort of PWECP treated with valproic acid at the onset of pregnancy showed that generalized tonic-clonic seizures or focal to bilateral tonic-clonic seizures during pregnancy were twice as likely to occur when valproic acid was removed or replaced with another ASM, compared to when it was maintained throughout the pregnancy.[2]

The serum concentration of most ASMs has a defined therapeutic window for effective seizure control. The serum concentration of some ASMs (in particular, lamotrigine and levetiracetam) decreases during pregnancy. These decreases may occur at any point during the pregnancy.[12,13,14]

There are limited data available on epilepsy-related outcomes during pregnancy among PWECP for numerous ASMs, including but not limited to acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, and vigabatrin.

Level	Recommendation
Level A	2A. Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal to bilateral tonic-clonic seizures) in PWECP during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus.
Level B	2B. Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal to bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid).

Level	Recommendation
Level B	2C. Clinicians should monitor ASM levels in PWECP throughout pregnancy as guided by individual ASM pharmacokinetics and patient clinical presentation.
Level B	2D. Clinicians should adjust the dose of ASMs at their clinical discretion during the pregnancy in response to 1) decreasing serum ASM levels, or 2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of ASMs in the pregnant state).
Level B	2E. Clinicians treating PWECP using acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs.

Antiseizure medications: Major congenital malformations

Recommendation 3

Rationale

The unadjusted birth prevalence of any major congenital malformation (MCM) among children born to people without epilepsy is approximately 2.4%–2.9%.[15] Of the ASMs with sufficient numbers of exposures to draw reliable conclusions (greater than 1,000 exposures), lamotrigine, levetiracetam, and oxcarbazepine are associated with the lowest unadjusted birth prevalence of any MCM in monotherapy (3.1%, 3.5%, and 3.1%, respectively) among children born to PWECP. Valproic acid exposure is associated with the highest unadjusted birth prevalence (9.7%) of any MCM among children born to PWECP as compared to other ASMs.

Valproic acid is associated with the highest unadjusted birth prevalence of neural tube defects (NTDs) (1.4%) as compared to other ASMs. Phenobarbital is associated with the highest unadjusted birth prevalence of cardiac malformations (4.4%) as compared to other ASMs. Phenobarbital and topiramate are associated with the highest unadjusted birth prevalence of oral and cleft palate (2.2% and 1.4% respectively) compared to other ASMs. Valproic acid is associated with the highest unadjusted birth prevalence of urogenital (1.2%) and renal (1.4%) malformations compared to other ASMs.

A detailed anatomical ultrasound of the fetus can enable earlier diagnosis of MCMs.[16,17,18,19,20] Early detection of severe congenital heart defects, especially those requiring surgery in the early postnatal period, has been shown to improve morbidity and mortality in affected newborns.[21,22,23,24] Detection of MCMs can also inform an early pregnancy termination decision or guide perinatal management, including giving birth in specialized pediatric centers, while a normal ultrasound may offer reassurance to expecting parents. This needs to be balanced with differences in individual preferences.

Level	Recommendation
Level A	3A. Clinicians must counsel their patients with epilepsy that the birth prevalence of any MCM in the general population is approximately 2.4%–2.9%, providing a comparison framework for their individual risk.
Level A	3B. Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs.
Level A	3C. Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs (composite outcome) or NTDs, if clinically feasible.
Level A	3D. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared to other studied ASMs.
Level A	3E. To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital in PWECP, if clinically feasible.
Level B	3F. To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate in PWECP, if clinically feasible.
Level B	3G. To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible.
Level B	3H. To enable early detection and timely intervention of MCMs, obstetricians should recommend fetal screening for MCMs (e.g., a detailed anatomical ultrasound, where available) for PWECP who are treated with any ASM during pregnancy.
Level B	3I. To enable early detection and timely intervention of congenital heart defects, obstetricians should recommend screening cardiac investigations of the fetus among PWECP who are treated with phenobarbital during pregnancy.

Antiseizure medications: Perinatal outcomes

Recommendation 4

Rationale

Among children exposed to ASMs in utero and born to PWECP, the prevalence of intrauterine death is highly likely not to differ across ASMs when used in monotherapy and the prevalence of prematurity is possibly no different across ASMs when used in monotherapy. The risk of intrauterine death is likely higher with polytherapy exposure compared to monotherapy exposure. Fetal growth restriction increases the risk of perinatal morbidity and mortality.[25,26] The prevalence of children being born small for gestational age (SGA) is possibly greater after exposure to valproic acid or topiramate compared to lamotrigine. Prenatal identification of fetuses at risk of being born SGA leads to improved perinatal outcomes by informing timely delivery.[27]

Level	Recommendation
Level B	4A. Clinicians should counsel PWECP that the prevalence of intrauterine death does not differ among different ASM exposures in monotherapy.
Level B	4B. Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born SGA, if clinically feasible.
Level B	4C. To enable early identification of fetal growth restriction, obstetricians should recommend screening of fetal growth throughout pregnancy among PWECP who are treated with valproic acid or topiramate.

Antiseizure medications: Neurodevelopmental outcomes

Recommendation 5

Rationale

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in full scale IQ at age 6 years compared to gabapentin and lamotrigine in monotherapy; valproic acid is possibly associated with a decrease as compared to carbamazepine, levetiracetam, and topiramate in monotherapy; and there is possibly no difference in full scale IQ with valproic acid as compared to phenytoin in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid is likely associated with a decrease in verbal IQ at age 6 years compared to gabapentin, lamotrigine, levetiracetam, and phenytoin in monotherapy, and possibly associated with a decrease as compared to carbamazepine and topiramate in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid is possibly associated with a decrease in non-verbal IQ at age 6 years compared to carbamazepine and phenytoin in monotherapy, but there is possibly no difference as compared to gabapentin, lamotrigine, levetiracetam, and topiramate in monotherapy.

Among children born to PWECP, in utero exposure to valproic acid throughout the pregnancy is possibly associated with an increased risk of autism spectrum disorder (ASD) and autistic traits compared to other studied ASMs (i.e., carbamazepine, clonazepam, lamotrigine, and levetiracetam) used in monotherapy.

Numerous ASMs have limited available data on neurodevelopmental outcomes. These neurodevelopmental outcomes are determined during both early and later stages of pregnancy.[28] Early screening for neurodevelopmental disorders in children enables early diagnosis, facilitating access to early interventions where available. Early interventions in children with neurodevelopmental disorders optimize developmental trajectories.

Level	Recommendation
Level A	5A. To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in nonpregnant PWECP, if clinically feasible.
Level A	5B. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is likely or possibly associated with a decrease in full scale, verbal, and non-verbal IQ, as compared to other studied ASMs (i.e., carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, and topiramate).
Level A	5C. Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is possibly associated with an increased risk of ASD as compared to other studied ASMs (i.e., carbamazepine, clonazepam, levetiracetam, and lamotrigine).
Level B	5D. Clinicians should implement age-appropriate developmental screening in children exposed to any ASM in utero born to PWECP.

Folic acid

Recommendation 6

Rationale

The optimal dosing and timing of folic acid supplementation is unknown in PWECP. There is likely no demonstrated benefit of folic acid supplementation (at least 0.4 mg/d) specifically for the prevention of MCMs in children born to PWECP. Randomized controlled trials conducted before widespread folic acid fortification of foods in the United States demonstrated a reduction in NTDs among the offspring of the general childbearing population receiving periconceptional multivitamin supplementation.[29] A systematic review of 14 studies of folic acid supplementation (up to 1 mg/d) among pregnant people in the general population (generally without epilepsy), including 1,053 participants (some being control participants without folic acid supplementation) estimated that folic acid supplementation of 0.2 mg/d (the United States' level of folic acid fortification), would reduce the risk of NTDs by 23%.[30] This protective effect was greater in pregnant people with an initial low serum folate concentration than in those with higher serum folate concentrations.[30] Although valproic acid exposure in utero is associated with the highest prevalence of NTDs, the teratogenic causal pathway is not exclusively through the disruption of folic acid metabolism.[31]

Preconception folic acid supplementation is possibly associated with better neurodevelopmental outcomes among children born to PWECP. Folic acid supplementation of at least 0.4 mg/d is possibly associated with reduced autistic traits at 3 years (OR 7.9, 95% CI 2.5–24.9) and likely associated with a higher global IQ (on average 6 points) at 6 years in children born to PWECP exposed to ASMs in utero. Lower plasma concentrations of folic acid at gestational weeks 17–19 among pregnant people with epilepsy exposed to ASMs is correlated with a higher risk of autistic traits at 3 years. Higher exposure levels of folic acid from diet and supplements is associated with statistically significant increases in IQ at age 6 years; this association is not seen among PWECP who only received dietary folic acid and did not receive periconceptional folic acid supplements. Higher doses of folic acid supplementation result in higher serum concentrations of folic acid.[32,33] There is inconclusive evidence

for an increased risk of adverse events with folic acid supplementation for the PWECP as well as the child (e.g., increased occurrence of twins, asthma, masking vitamin B12 deficiency, new or worsening of pre-existing neoplasia).[29,34,35] In a recent analysis of 27,784 children born to people with epilepsy, exposure to periconceptional folic acid greater than 1 mg/d was associated with a 0.9% absolute increase in the risk of childhood cancer before age 20 years, resulting in an HR of 2.7 (95% CI 1.2–6.3).[35] There are potential pharmacokinetic interactions where folic acid can decrease phenytoin serum concentrations.[36] Adherence to folic acid supplementation is generally poor among PWECP, even during pregnancy.[37] ASM polytherapy is associated with decreased folic acid adherence among PWECP.[38] In the United States, where there is no high-dose folic acid formulation, higher doses of folic acid require a large number of tablets, potentially reducing adherence to folic acid supplementation.

Level	Recommendation
Level B	6A. Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs in the offspring.
Level A	6B. Clinicians must prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring.
Level B	6C. Clinicians should counsel PWECP treated with an ASM that adherence to recommended folic acid supplementation preconceptionally and during pregnancy is important to minimize the risk of MCMs and poor neurodevelopmental outcomes.

This practice guideline was endorsed by the Child Neurology Society.

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