REVIEW

Epilepsy during pregnancy: focus on management strategies

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Abstract: In the US, more than one million women with epilepsy are of childbearing age and have over 20,000 babies each year. Patients with epilepsy who become pregnant are at risk of complications, including changes in seizure frequency, maternal morbidity and mortality, and congenital anomalies due to antiepileptic drug exposure. Appropriate management of epilepsy during pregnancy may involve frequent monitoring of antiepileptic drug serum concentrations, potential preconception switching of antiepileptic medications, making dose adjustments, minimizing peak drug concentration with more frequent dosing, and avoiding potentially teratogenic medications. Ideally, preconception planning will be done to minimize risks to both the mother and fetus during pregnancy. It is important to recognize benefits and risks of current and emerging therapies, especially with revised pregnancy labeling in prescription drug product information. This review will outline risks for epilepsy during pregnancy, review various recommendations from leading organizations, and provide an evidence-based approach for managing patients with epilepsy before, during, and after pregnancy.

Keywords: epilepsy, teratogens, anticonvulsants, medication therapy management

Introduction

Epilepsy is a common chronic disorder affecting approximately over one million women of childbearing age.[1–3] Reproductive function can negatively impact women with epilepsy (WWE) by decreasing fertility, increasing the risk of polycystic ovary syndrome, abnormal menstrual cycles, and altered antiepileptic drug (AED) metabolism.[2] For WWE who become pregnant, ~24,000 babies are born each year.[3] While over 90% of these women have healthy babies, there are specific concerns for WWE, in whom the disorder may significantly impact the health of the mother and the fetus.[4] With numerous issues and needs to address for WWE during pregnancy, health care is often fragmented with few medical groups providing joint obstetric–epilepsy care.[5] An individualized approach delivered by a team of neurologists, obstetricians, primary care doctors, nurses, and clinical pharmacists with knowledge of various aspects of epilepsy in pregnancy is needed to improve outcomes in pregnant patients with epilepsy. This article aims to provide essential knowledge and effective medication management strategies to care for WWE before, during, and after pregnancy. It is important to note that several other nonpharmacological issues may need to be addressed in WWE, such as previous obstetric and psychiatric history, but are outside the scope of this review.

Risks and complications in pregnant WWE

Although a majority of WWE (54%–80%) will not experience a change in seizure frequency during pregnancy, seizure frequency and severity may increase in 15%–32%

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of WWE as estrogen and progesterone can alter neuronal excitability and affect the seizure threshold.[1,6–8] Therefore, seizure control prior to pregnancy is one of the best predictors of seizure control during pregnancy. Women who are seizure-free in the 9 months prior to pregnancy have an 84%–92% chance of remaining seizure-free during pregnancy on their current regimen.[1]

Another factor for WWE who become pregnant is an increased risk of maternal mortality. Maternal mortality is ten times higher in WWE than in those without the disorder.[9] In a retrospective cohort study 69,385 WWE and 20,449,532 without epilepsy, the risk of death in WWE during delivery hospitalization was 80 per 100,000 pregnancies and was significantly higher than 6 deaths per 100,000 pregnancies in women without epilepsy (adjusted odds ratio [OR], 11.46 [95% confidence interval [CI], 8.64–15.19]).[10] WWE also had increased risk of other adverse outcomes, including preeclampsia (adjusted OR, 1.59 [95% CI, 1.54–1.63]), preterm labor (adjusted OR, 1.54 [95% CI, 1.50–1.57]), and stillbirth (adjusted OR, 1.27 [95% CI, 1.17–1.38]), and increased health care utilization, including an increased risk of cesarean delivery (adjusted OR, 1.40 [95% CI, 1.38–1.42]) and prolonged length of hospital stay (>6 days) among women with cesarean deliveries (adjusted OR, 2.13 [95% CI, 2.03–2.23]) and vaginal deliveries (adjusted OR, 2.60 [95% CI, 2.41–2.80]).[10] Other obstetrical complications that have been observed in WWE include bleeding in pregnancy, excessive bleeding postpartum, preterm birth, and small for gestational age.[11] A systematic review of 38 studies in low- and high-income countries found that WWE (2,837,325 pregnancies) had increased risks of spontaneous miscarriage (OR 1.54, 95% CI 1.02–2.32; I^2=67%), antepartum hemorrhage (OR 1.49, 95% CI 1.01–2.20; I^2=37%), postpartum hemorrhage (OR 1.29, 95% CI 1.13–1.49; I^2=41%), hypertensive disorders (OR 1.37, 95% CI 1.21–1.55; I^2=23%), induction of labor (OR 1.67, 95% CI 1.31–2.11; I^2=64%), cesarean section (OR 1.40, 95% CI 1.23–1.58; I^2=66%), any preterm birth (<37 weeks of gestation; OR 1.16, 95% CI 1.01–1.34; I^2=64%), and fetal growth restriction (OR 1.26, 95% CI 1.20–1.33; I^2=1%) compared with women without epilepsy (2,809,984 pregnancies).[12] Outcomes that did not differ between women with and without epilepsy included early preterm birth, gestational diabetes, fetal death or stillbirth, perinatal death, or admission to neonatal intensive care.

Children who are born to WWE have a higher risk of birth defects, likely related to in utero exposure to AEDs. Specifically, WWE have a 4%–14% chance of giving birth to a child with a major malformation, compared with 1%–4% in the general population.[2,13] Major malformations associated with exposure to AEDs include cleft lip and palate, ventricular septal defect, neural tube defects, and minor abnormalities that include hypertelorism, epicanthal folds, broad nasal bridge, elongated philtrum, distal digital, and nail bed hypoplasia.[1,2] The risk of malformation appears to be different for individual AEDs and can be related to dose.

One of the most important issues related to birth defects caused by AED exposure is the ability of the provider to appropriately assess risks and complications that may occur. In 2014, the US Food and Drug Administration (FDA) published the "Pregnancy and Lactation Labeling Rule" (PLLR or Final Rule), which required changes to the content and format of information presented in the prescription drug labeling (eg, package insert).[14] The pregnancy subsection removed the pregnancy letter categories (A, B, C, D, X) and required (rather than recommended) information about pregnancy exposure registries and now includes subheadings of risk summary, clinical considerations, and data. Other subsections that will be included in the PLLR include lactation and females and males of reproductive potential. The intention of these changes was to assist health care providers in evaluating benefit versus risk and in counseling pregnant women and nursing mothers who need to take medication and allow them to make informed and educated decisions for themselves and their children.

Therefore, the presence of epilepsy and exposure to AEDs presents a small, yet significant association with adverse outcomes in pregnancy. These increased risks and data regarding each drug should be considered when discussing reproductive health and conception planning for WWE.

Management issues in the treatment of epilepsy before and during pregnancy
Medication considerations

Medication therapy is the mainstay of treatment in patients with epilepsy; however, ~50% of patients will continue to have seizures following initiation of their first AED.[15,16] This often leads to either switching to an alternative medication or the addition of an adjunctive AED. These treatment challenges are especially problematic in WWE who are pregnant or are planning to become pregnant. Ideally, prior to contraception, being seizure-free for at least 9–12 months is a relatively good predictor of freedom from seizure throughout the pregnancy.[17–19] However, this predictor is dependent

upon AED drug serum concentrations staying within 35% of the preconception value throughout the pregnancy.[20] This can be challenging due to the potential for significant pharmacokinetic changes during pregnancy, such as marked increases in clearance and volume of distribution.[20] Several AEDs have been documented to have increases in clearance that has led to decreased serum concentrations, which has resulted in increased seizure frequency. More frequent monitoring of serum drug concentrations and patient education can be a valuable tool when managing a pregnant WWE.[21]

Monotherapy versus polytherapy

One important preconception goal is the utilization of medication monotherapy versus polytherapy. This recommendation is supported by the American Academy of Neurology and the American Epilepsy Society in their practice parameter update of management issues in pregnant WWE.[1] It was previously thought that AED polytherapy should always be avoided during pregnancy because prior studies showed a higher rate of major congenital malformations. It was found in the North American Antiepileptic Drug Pregnancy Registry that including valproate in these regimens was a major influence on these data and exposure to other combinations

of AEDs was similar to rates seen in monotherapy.[22] Therefore, using specific polytherapy combinations with less teratogenic risk (eg, levetiracetam and lamotrigine) should be considered prior to initiating valproate for idiopathic or genetic generalized epilepsy.

When possible, using monotherapy prior to and during pregnancy is preferred because it can reduce the risk of long-term poor cognitive outcomes in the offspring that was associated with polytherapy.[23–26] A key part of preparing a WWE for pregnancy involves trying to identify the minimum therapeutic dose (and corresponding level) that is able to control her seizures. As mentioned earlier, polytherapy has also been associated with higher malformation rates.[27] There are some AEDs, such as valproate and phenobarbital, that possess more risk of causing clinical malformations and cognitive impairment than others, and the benefits rarely outweighs the risks. Additionally, some AEDs lack extensive human data and evaluation of animal data, small observational studies, and anecdotal data is needed to guide treatment decisions. Despite monotherapy offering notably lower risks during pregnancy, each individual AED possesses its own associated teratogenicity risk when used as monotherapy and should be considered on an individual patient basis (Table 1).

Table 1 AED pregnancy category and risk

Drug name	Previous FDA pregnancy category[a]	Documented pregnancy outcomes
AZA[42–46,b]	C	One case of congenital glaucoma, microphthalmia, and patent ductus arteriosus One case of sacrococcygeal teratoma One case of metabolic complications postpartum (metabolic acidosis, hyperbilirubinemia, hypocalcemia, and hypomagnesemia) Animal studies: ureter and kidney abnormalities in mice; vertebral malformations occurred more frequently when dose was higher in rabbits
BRV[47]	C	There are limited amount of data in pregnant women Animal studies did not detect any teratogenic potential
CBZ[48–53]	D	EURAP Registry: 2% rate of MCM with <400 mg/d: neural tube defects, spina bifida, hypospadias, craniofacial defects, cardiovascular malformations No strong evidence of increase in MCM compared to general population Developmental delays
CLB	C	Withdrawal symptoms Animal studies: neurobehavioral and immunological function defects, decreased fetal body weights, and increased incidences of visceral and skeletal malformations
CZP[54]	D (US) C (AUS)	Withdrawal symptoms Animal studies: cleft palates
Diazepam[55–61]	D	Congenital malformations and developmental abnormalities One case of OEIS complex Low birth weight Withdrawal symptoms (three cases)
Divalproex sodium (VPA)	X	See valproic acid
ESL[62]	C	Animal studies: teratogenicity, developmental delays, skeletal abnormalities, and fetal growth retardation

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Table I (*Continued*)

Drug name	Previous FDA pregnancy category[a]	Documented pregnancy outcomes
ESM[63–68]	Not formally assigned (pregnancy risk factor C)	Cases of hemorrhage in the neonate, patent ductus arteriosus, cleft lip/palate, hydrocephalus
		Significant increase in MCM risk when coadministered with phenobarbital
EZG (Retigabine)	C	Animal studies: pre- and postnatal mortality, growth deficit, developmental toxicity
FBM[69–71]	C	Animal studies: higher death rate and decreased body weight
GBP[72–75]	C	One MCM out of 59 exposures (1.7%) in Danish cohort
		Animal studies: delayed ossification, impaired synaptogenesis
LAC[76]	C	Animal studies: pre- and postnatal mortality, growth deficit
LTG[56,73,77–80]	C (immediate release)	No strong evidence of facial cleft compared to general population
	D (XR)	EURAP study: lowest MCM rate (1.7%) among AED with exposure <300 mg/day
		The malformation rate was 5.2% in the Australian Registry
		The MCM rate was 3.7% in Denmark cohort
LVT[23,73,80–83]	C	Only two MCM (0.7%, inguinal hernia and reflux requiring surgery) out of 304 first trimester exposures in UK; 2.4% MCM in US; 0 MCM out of 22 exposures in Australia; 0 MCM out of 58 exposures in Danish cohort
		Animal studies: structural and developmental toxicity
Lorazepam[84,85]	D (US)	Withdrawal symptoms
	C (AUS)	Cases of anal atresia
Methsuximide[86]	Not formally assigned (pregnancy risk factor C)	Insufficient evidence regarding birth defect risk
OXC[73,87–89]	C (US)	2.8% MCM were seen in Danish cohort
	D (AUS)	Animal studies: developmental toxicity, malformations, embryo fetal death, decreased fetal body weight
PER[90]	C	Animal studies: visceral abnormalities, embryo lethality, reduced fetal body weight, and embryo-fetal developmental toxicity
PB[91–93]	D	Teratogenicity (first trimester): heart defects and facial clefts
		Withdrawal symptoms (third trimester)
Phenytoin/Fosphenytoin[91–101] (PHT)	D	Fetal hydantoin syndrome, cases of orofacial clefts, cardiac defects, microcephaly, developmental delay, malignancies (neuroblastoma)
PGB[102,103]	C	One case of malformation (out of 30) in one study
		Animal studies: structural and developmental abnormalities
PRM[104,105]	Not assigned	Cases of neonatal hemorrhage
		Animal studies: dose-related cleft palate
RUF[106]	C	Animal studies: decreased fetal weights and increased incidences of fetal skeletal abnormalities, observed in cases of maternal toxicity
TGB[107]	C	Animal studies: high doses teratogenic effect
TPM[23,73,80,108–110]	D	Cleft lip or palate (1.4% in US, 2.2% in UK, both ~ten-fold the general population), hypospadias
		Small for gestational age (lower birth weight and shorter length): seems 1.8- to 3.3-fold more likely to happen than with lamotrigine
		One malformation out of 31 exposures (3.2%) was seen in the Australian Registry
		4.6% MCM were seen in Danish cohort
VPA[23,26,53,57,80,111–131]	X	Strong evidence of human teratogenicity: neural tube defects, higher rate of spina bifida (1%–2%) than other AEDs, craniofacial defects (cleft palate), malformations of the limbs, cardiovascular malformations (atrial septal defects), hypospadias
		MCM reported 6%–9% (fourfold compared to any monotherapy)
		Increased risk of MCM both when used in monotherapy and polytherapy
		Dose-related risk of MCM (6% under 700 mg/day, 10% between 700 and 1,500 mg/day, >20% above 1,500 mg/day)
		Developmental delay: lower IQ scores (verbal more than nonverbal) compared to no AED or monotherapy, increased risk of ADHD at age 6 years
		Withdrawal syndrome if taken during the third trimester
		Cases of hypoglycemia and hypothyroidism

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Table 1 (*Continued*)

Drug name	Previous FDA pregnancy category[a]	Documented pregnancy outcomes
VGB[132,133]	C	Cases of congenital malformations (eg, cardiac, genital, and renal defects)
		Two cases of visual field loss in children (6- and 7-year-old) exposed in utero
ZNS[109,134,135]	C	Small for gestational age (lower birth weight and shorter length): seems 0.9 to 2.8-fold more likely to happen than with lamotrigine
		One case of anencephaly and one case of atrial septal defect

Notes: [a]FDA pregnancy category definitions: A – Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). B – Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. C – Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. D – There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. X – Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. [b]Used in epilepsy; however, not an AED.
Abbreviations: AED, antiepileptic drug; ADHD, attention-deficit hyperactivity disorder; AZA, acetazolamide; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESL, eslicarbazepine acetate; ESM, ethosuximide; EZG, ezogabine; FDA, Food and Drug Administration; FBM, felbamate; GBP, gabapentin; LAC, lacosamide; LTG, lamotrigine; LVT, levetiracetam; MCM, major congenital malformations; OEIS, omphalocele-exstrophy-imperforate-anus-spina bifida; OXC, oxcarbazepine; PER, perampanel; PB, phenobarbital; PGB, pregabalin; PRM, primidone; RUF, rufinamide; TGB, tiagabine; TPM, topiramate; VPA, valproic acid; VGB, vigabatrin; ZNS, zonisamide.

As expected, there is dose-dependent teratogenicity risk within individual drugs; however, this has only been documented with valproate and more recently topiramate.[27] Additionally, in polytherapy, teratogenicity risks have been associated with drug combinations that were not documented when each individual drug was used as monotherapy. When used in polytherapy, the malformation rate of topiramate dramatically increases to 14.1% versus 2.4% when used as monotherapy.[25,27] This was recently reported in the Australian Pregnancy Registry but had not been reported prior.[27] It is important to put the risk of teratogenicity into perspective; in general, the risk of significant fetal malformation is approximately 3% if one AED is prescribed and up to approximately 17% if polytherapy is recommended.[28,29] Drug teratogenicity risk should be routinely considered throughout pregnancy when treating a WWE.

Once a WWE has conceived, appropriate evaluation and counseling should continue along with frequent risk–benefit pharmacotherapy evaluations and monthly AED serum concentrations. In the US, it is common practice to recommend a level II ultrasound at 18–20 weeks gestational age for women taking AEDs during pregnancy. This is a detailed anatomic evaluation, which provides very high sensitivity for structural abnormalities affecting the fetus (>95% for neural tube defects in most laboratories).[30] As previously discussed, abrupt discontinuation of AED is not recommended solely to minimize fetal exposure. Abrupt discontinuation of any AED possesses an increased risk of status epilepticus and sudden unexpected death in epilepsy. Due to a high risk of teratogenicity and cognitive impairment with valproate and phenobarbital, these two AEDs should never be initiated

in a pregnant patient or women of childbearing potential. However, in women with difficult-to-treat seizures who are clinically stable on one of these drugs and are already pregnant upon presentation, some clinicians may opt to continue the drug throughout pregnancy as opposed to abrupt discontinuation.

One example of a newer AED that appears to have an intermediate risk of teratogenicity is topiramate.[25,27] Lower teratogenic risk appears to present for lamotrigine and levetiracetam, which are commonly employed as medication therapy during pregnancy.[25,27] It is important to note that both lamotrigine and levetiracetam have a very high clearance in the second and third trimesters, which has led to the need for significantly higher doses, not seen in patients who are not pregnant. Serum concentrations of all AEDs should be followed on a regular basis, including a bound level for all AEDs that are highly protein bound.[29]

Brand versus generic AEDs

Current guidelines do not address or recommend switching from brand to generic AEDs in pregnant patients due to the possibility of disrupting the stable state of the patient by the increased risk of seizures. However, it has been shown that there was no increase in hospitalizations and all cause emergency department visits when patients switched from brand to generic lamotrigine, divalproex, and phenytoin.[31] Despite this, there are often issues with the utilization of AEDs, which is why it is often recommended that AEDs not be switched from brand to generic. This is represented in incidences where brand phenytoin was switched to generic and dose adjustments and/or the addition of another AED were

necessary.[31] Furthermore, the most commonly used AED in pregnancy is lamotrigine since it is associated with the lowest risk of fetal malformations compared to other AEDs.[23] Recently, a couple of FDA bioequivalence studies supported switching from brand to generic lamotrigine in patients with epilepsy.[32,33] These studies did not include pregnant patients or make a recommendation for its use in this special population. Additionally, the American Epilepsy Society published a position statement regarding generic substitution of AEDs without a recommendation for patients with epilepsy who are pregnant.[34] Therefore, it is currently unknown if generic substitution is appropriate in patients with epilepsy who are pregnant.[32,33]

Ideally, safe and effective medication selection should occur prior to pregnancy; use of monotherapy and frequent serum AED concentrations monitoring will decrease the risk of dose-related teratogenicity and decrease the risk of complications from increased seizure frequency.

Counseling and education: risk–benefit assessments and use of guidelines

Benefit and risk assessments for WWE who want to become pregnant should begin prior to conception. Preconception planning, including adequate contraception, proper

counseling, and good clinical disease management, is essential in WWE to mitigate any fetal or maternal risk. Practitioner-initiated education and counseling in women of childbearing potential should be a top priority. Common misconceptions surrounding pregnancy in WWE have led to permanent sterilization so as to not genetically pass on the disease, fear of pregnancy causing increased seizure frequency leading to poor fetal/maternal outcomes, and lack of breastfeeding. Several organizations have included recommendations of counseling and education points that should be reviewed when discussing conception and pregnancy with WWE (Table 2). These guidelines and recommendations are largely based around appropriate education and counseling, and less on medication therapy management.

There should also be a discussion about preconception folic acid supplementation and vitamin K supplementation at birth. There are currently no commonly accepted and consistent standards (Table 2) specific to WWE and the recommendation for folic acid. This has led to practitioners supplementing patients using their own discretion. However, in most practices in the US, WWE planning pregnancy are given the recommendation of 400 mcg daily of folic acid. When they become pregnant, if they have no history or family history of neuronal tube defects (eg, spinal bifida) and are not

Table 2 Recommendations for epilepsy and pregnancy

Topic	AAN/AES[1]	UK NICE guidelines[136]	ETDP – EFA[137]
Year of publication	2009	2012 (update 2016)	2007
Counseling on seizure-induced harm during pregnancy	**Tonic–clonic seizures:** Not mentioned	**Tonic–clonic seizures:** Relatively higher risk of harm to fetus	**Tonic–clonic seizures:** Can particularly increase the risk of brain or other injuries, congenital malformations, and developmental delay (verbal IQ affected by seizure frequency) in the fetus
	Status epilepticus: Possible in 0%–1.8% of WWE	**Status epilepticus:** Can possibly occur	**Status epilepticus:** Poses risks of maternal and fetal survival, excellent seizure control is therefore needed, particularly for complex partial and tonic–clonic seizures
	SUDEP: Not mentioned	**SUDEP:** Possible	**SUDEP:** Not mentioned
Counseling on seizure frequency during pregnancy	**Increase in seizure frequency:** Might occur in 14%–32% of WWE	**Increase in seizure frequency:** Not likely to occur	**Increase in seizure frequency:** Occur in one-fourth to one-third of WWE
	Seizure freedom at least 9 months prior to pregnancy: Probably associated with a high likelihood (84%–92%) of remaining seizure-free during pregnancy	**Seizure freedom at least 9 months prior to pregnancy:** Not mentioned	**Seizure freedom at least 9 months prior to pregnancy:** Not mentioned
	Frequency of tonic–clonic seizures: May affect the risk of harm to the fetus	**Frequency of tonic–clonic seizures:** Not mentioned	**Frequency of tonic–clonic seizures:** Not mentioned

(*Continued*)

Table 2 (*Continued*)

Topic	AAN/AES[1]	UK NICE guidelines[136]	ETDP – EFA[137]
Counseling on risks for pregnant WWE	There is probably no more than a 1.5-fold increased risk of premature contraction, labor, or delivery, but there is possibly more than a twofold increase in such risk in WWE who smoke Probably increased risk of SGA and possibly at increased risk of 1-minute Apgar scores of <7 Probably no increased risk of late pregnancy-related bleeding complications, insufficient evidence for hemorrhagic complications in the newborn	More likely to have complications during pregnancy and labor	In some studies, WWE have an increased risk of vaginal bleeding, hypertension, preeclampsia, antepartum hemorrhage, and cesarean delivery Higher-than-expected rates of preterm delivery, failure to progress, and cesarean section are still evident in WWE 95% of WWE have a safe normal delivery without a seizure; generalized epilepsy women are more likely than those with partial epilepsy to have a seizure at this time WWE are more likely to have labor induced, abruptio placentae, cesarean sections, and maternal death around delivery (tenfold for the latter but risk still low 8/10,000)
Prenatal screening	Not mentioned	Pregnant women and girls who are taking AEDs should be offered a high-resolution ultrasound scan at 18–20 weeks of gestation by an appropriately trained ultrasonographer, but earlier scanning may allow MCM to be detected sooner	Ultrasound at 11–13 weeks is recommended to rule out neural tube defects (along with serum alpha-fetoprotein at 16 weeks) and other MCM Ultrasound at 18–22 weeks to determine cardiac development, head and spine anatomy, and cleft lip or cleft palate
Dose of AED	Dose of VPA and LTG should be limited since it is correlated to MCM	Lowest effective dose for each AED	Seizure control with the minimum effective AED dose is the goal, minimizing fetal exposure to AED
Polytherapy	**Should be avoided:** During the first trimester to prevent MCM Throughout pregnancy to prevent cognitive impairment, especially when VPA is included	**Should be avoided**	**Monotherapy is preferable** whenever possible, while still maintaining good seizure control VPA is most likely to induce malformations when used as polytherapy
Monitoring of AED serum levels	Should be considered routinely for LTG (seizure frequency is probably increased when 65% of target level is reached), CBZ, and PHT may be considered routinely for OXC and LVT Not enough evidence for other AED	Recommended if seizures increase or are likely to increase Recommended if dose needs to be adjusted Not recommended otherwise in routine Lamotrigine and phenytoin are at risk of low serum levels	Careful monitoring of AED levels is needed throughout pregnancy AED levels should be monitored closely in the weeks following delivery since they may increase gradually LVT, OXC, and LTG showed elevated levels with days of delivery
Folic acid administration	**Time frame:** Prior to conception and during pregnancy may be considered to prevent MCM **Dose:** At least 0.4 mg/day	**Time frame:** Before any possibility of pregnancy **Dose:** 5 mg/day	**Time frame:** Before conception and throughout pregnancy **Dose:** 0.4 mg/day for nonpregnant women, 0.6 mg/day for pregnant women and those contemplating pregnancy, and 0.5 mg/day for lactating women. Many epileptologists recommend higher doses (0.8–4 mg/day) for women with epilepsy. However, for women with a family history of a neural tube defect, 4 mg/day is the recommended dosage

(*Continued*)

Table 2 (*Continued*)

Topic	AAN/AES[1]	UK NICE guidelines[136]	ETDP – EFA[137]
Vitamin K administration	**To pregnant WWE:** Insufficient evidence to support supplementation	**To pregnant WWE:** Not mentioned	**To pregnant WWE:** Oral dose of 10–20 mg/day suggested during the last month of pregnancy, especially if taking enzyme-inducing AED
	Neonates: Not mentioned	**Neonates:** All children born to mothers taking enzyme-inducing AEDs should be given 1 mg parenterally at delivery	**Neonates:** 1 mg IM or IV at birth besides monitoring for bleeding
Specific use of VPA	**Risk summary and recommendations:** Avoidance during the first trimester should be considered to decrease the risk of MCM (neural tube defects, facial clefts, and hypospadias) VPA is very likely to induce more MCM than CBZ, and possibly PHT and LTG, so VPA should be avoided VPA is probably associated with poor cognitive outcomes, probably more than CBZ and possibly more than PHT, so VPA should be avoided	**Risk summary and recommendations:** Should not be used unless other therapies are ineffective or not tolerated; patient should be counseled on the risk of malformations and developmental impairments	**Risk summary and recommendations:** VPA has been shown to carry a high risk of spina bifida aperta, cardiovascular complications, urogenital malformations, and skeletal defects VPA has been shown to decrease verbal IQ (22% of children had mental retardation versus 7% in unexposed)
	Dose-dependent risk: Not mentioned	**Dose-dependent risk:** Greater risk with doses >800 mg/day	**Dose-dependent risk:** VPA is most likely to induce malformations when used above doses of 1,000 mg/day; decrease in verbal IQ is dose-dependent
	Polytherapy: Higher evidence of such risk if VPA is taken as part of polytherapy AED	**Polytherapy:** Greater risk	**Polytherapy:** Not mentioned
Specific use of other AED	**Older AED:** CBZ, PHT, PB: avoidance may be considered to reduce the risk of cleft palate (PHT and CBZ), cardiac malformations (PB), and poor cognitive outcomes (PHT and PB)	**Older AED:** Not mentioned	**Older AED:** Barbiturates have been found to be associated with MCM PHT has been associated with facial clefts, congenital heart, and urogenital defects CBZ has been associated with neural tube defects, heart defects, hypospadias, hip dislocations, and inguinal hernia
	Newer AED: Not enough data to assess teratogenicity and make recommendations		**Newer AED:** Lamotrigine has the most data available at this time, with possibly no substantially increased risk of MCM Preliminary studies have found a good pregnancy safety profile with levetiracetam, but more data are needed

Abbreviations: AED, antiepileptic drug; AAN, American Academy of Neurology; AES, American Epilepsy Society; CBZ, carbamazepine; ETPD – EFA, Epilepsy Therapy Development Project – Epilepsy Foundation of America; IM, intramuscular; LTG, lamotrigine; LVT, levetiracetam; MCM, major congenital malformations; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SUDEP, sudden unexpected death in epilepsy; VPA, valproic acid; WWE, women with epilepsy.

on an AED commonly associated with neuronal tube defects, they should be on folic acid 400–800 mcg daily. If the women has a history or family history of neuronal tube defects, it is generally recommended that they be started on folic acid 4 mg 1 month prior to conception and continue throughout

their pregnancy. Some practitioners will use 4 mg per day of folic acid if a women is pregnant and on an AED that has been associated with neuronal tube defects (ie, valproic acid, carbamazepine, and gabapentin) in the absence of a history or family history of spinal bifida. If a woman has yet to

conceive, and is willing to optimize pharmacotherapy prior to conception, a medication review should be done to make sure that she is not on valproate or any other potentially teratogenic medication (all medications in regimen). An attempt to ensure she is on the least number of AEDs at the lowest effective doses is also warranted.

The risk of passing epilepsy to the child is very low; however, in specific cases, there is a risk of idiopathic generalized epilepsy, which is ~5%–20% (one affected first-degree relative) and >25% (two first-degree relatives) affected. The overall risk of a mother passing on idiopathic generalized epilepsy is 9%–12%.[28,35]

Overview on the current and emerging therapies

Until recently, it was generally accepted that the newer AEDs were as effective as the older first-generation AEDs to prevent seizure. Recent data from the Australian Pregnancy Registry revealed that newer AEDs, such as topiramate and lamotrigine, were associated with increased seizure frequency during pregnancy; however, this was not statistically significant.[27] This observational trend does warrant further AED efficacy studies in the pregnancy setting.

The knowledge we have on risks during pregnancy for WWE taking newer and emerging therapies is very limited and is mostly based on Phase III premarketing clinical trials; this needs further assessment. Such an assessment will likely be based on data provided by various pregnancy and epilepsy registries, such as the North American AED Pregnancy Registry, the Australian Pregnancy Register for Antiepileptic Medication, the UK Epilepsy and Pregnancy Register, and The International Registry of AED and Pregnancy. Table 3 lists websites to access these pregnancy registries.

The International Registry of AED and Pregnancy was originally European-based and created in 1999 by a consortium of independent research groups, and later extended to 42 countries in Europe, Oceania, Asia, Latin America, and Africa. It is a large prospective observation study for women taking AEDs while pregnant, as it includes data obtained from other registries, including the Australian and the UK Register, but not the North American AED Pregnancy Registry. In the International Registry of AED and Pregnancy, all women taking AEDs at conception are eligible for inclusion whether the indication for treatment is epilepsy or other disorders. To avoid selection bias, only pregnancies enrolled before fetal outcome are known and within 16 weeks of gestation contribute to the prospective study. The primary objective is to compare the safety of different AEDs during pregnancy with respect to the risk of birth defects. Secondary objectives of the study are to establish the pattern of major malformations associated with AED, evaluate dose–effect relationships, and delineate drug-specific syndromes.

Similarly, in the North American Registry, the major objective is to obtain and publish information on the frequency of major malformations, such as heart defects, spina bifida, and cleft lip, among infants whose mothers had taken one or more AEDs to prevent seizures or to treat any other medical condition. It is also a prospective study, therefore, only findings in women who have enrolled before having any prenatal screening are used, to avoid bias of retrospective data. If a patient enrolls, a phone interview will be conducted at enrollment, at 7 months of gestation, then after delivery.

Enrollment in pregnancy registries is voluntary and at the discretion of the patient and/or provider (depending on the specific registry). While the management of pregnant WWE should include counseling on risks of various AEDs, women taking newer AEDs and emerging therapies with very little information regarding potential risks and birth defects should consider collaborating with their health care providers to enroll into a registry. Indeed, the success of registries greatly depends on patients' enthusiasm, putting provider and pharmacist counseling at the center of care of pregnant WWE. Counseling regarding registry participation may be included in a specialty pharmacy program and/or be part of multidisciplinary approaches (with physicians, nurses, and pharmacists) for the care of pregnant WWE. Such approaches have proven efficacious in multiple sclerosis for adherence to disease-modifying therapies and may improve patient adherence to pregnancy registries.[36,37] A specialty pharmacist in the ambulatory care neurology team may enhance patient education efficacy and recommendations from a clinical pharmacy specialist should be implemented into clinical decisions; more studies should be conducted to verify this hypothesis.

Table 3 Websites for various pregnancy registries

Name of pregnancy registry	Website
The North American AED Pregnancy Registry	www.aedpregnancyregistry.org/
Australian Pregnancy Register for Women on Antiepileptic Medication	www.epilepsy.org.au/research/ australian-pregnancy-register
UK Epilepsy and Pregnancy Register	www.epilepsyandpregnancy.co.uk
The International Registry of AED and Pregnancy (EURAP)	www.eurapinternational.org

Abbreviation: AED, antiepileptic drug.

Approach to WWE after pregnancy

Issues related to breastfeeding and epilepsy medications are outside the scope of this article; however, it is important for providers to collaborate with the patient after pregnancy so that AED medications are continued effectively and the most appropriate contraception can be provided. Once an infant is born, the AEDs taken by the mother need to be converted back to baseline dosage(s) due to the immediate changes in volume of distribution and protein binding after labor and delivery.[38] Additionally, it may be necessary for providers to communicate with each other to ensure that patients have highly effective contraception that is compatible with their antiepileptic treatment and to avoid unintended pregnancies, which put patients at high risk of poor outcomes. The Center for Disease Control and Prevention has published the United States Medical Eligibility Criteria to assist health care providers when counseling women, men, and couples about contraceptive method choice.[39] Specifically for WWE, the United States Medical Eligibility Criteria provides guidance on the safety of contraceptive method use with epilepsy and specific AEDs to avoid drug interactions that may decrease contraceptive efficacy. Revised recommendations were published for women in the immediate postpartum period (<42 days) regarding the use of combined hormonal contraceptives.[40] Additionally, one of the quality measures developed by the American Academy of Neurology includes counseling for women of childbearing potential (12–44 years) with epilepsy.[41] This measure is one of seven measures intended to facilitate quality improvement activities by recommending that providers give counseling at least once a year about how epilepsy and its treatment may affect contraception or pregnancy and should include a discussion about folic acid supplementation, contraception, potential antiseizure medications effect(s) on pregnancy, safe pregnancies, and breastfeeding.

Conclusion

WWE who desire pregnancy or become pregnant warrant special consideration and attention. These women have an increased risk of mortality and complications during pregnancy and labor including vaginal bleeding, preeclampsia, premature delivery, and cesarean delivery. Children who are born to WWE have a two- to threefold higher risk of major congenital malformations compared to the general population, which is likely related to in utero exposure to AEDs. The recent changes in pregnancy labeling by the FDA will allow for more critical evaluation by physicians, nurses and

pharmacists regarding potential risks to mothers and their children, which will encourage shared treatment decisions.

Medication management issues include choosing initial therapy for WWE of childbearing potential with lower teratogenic potential, routinely monitoring for efficacy, and selecting monotherapy regimens when possible. Valproate is the drug with the most evidence for inducing major malformations and impairment and should be avoided during pregnancy, either as monotherapy or polytherapy. Data suggest that polytherapy with AEDs other than valproate (eg, lamotrigine and levetiracetam in combination) are as safe as monotherapy. Lamotrigine has the most evidence among newer AED of safest use during pregnancy, but possibly has still more risks of malformations than the general population. Topiramate showed intermediate risk of malformations with facial/palate cleft outcomes among the newer AEDs. Switching brand to generic AED is not recommended based on precaution principle, even though hospitalization rates were not increased when doing so. Finally, folic acid supplementation is recommended in WWE before conception and throughout pregnancy at a minimum dose of 0.4 mg/day (4 mg/day if family history of neural tube defect, or on valproic acid, carbamazepine, or gabapentin).

Seizure frequency is not likely to increase during pregnancy, and being free of seizure 9–12 months prior to pregnancy is a good predictor of freedom from seizure during pregnancy. This success is largely dependent on AED serum concentrations, which should be monitored closely prior to and throughout pregnancy. Seizure control with the lowest effective dose of AED should be the goal and anticipated ahead of conception.

Limited data on newer and emerging AED suggest that international epilepsy and pregnancy registries are promising tools to prospectively assess birth defect risks. These registries may also be beneficial for tracking impact of older AEDs that were assigned the former FDA pregnancy category C where evidence has been lacking. It is important to encourage patient and/or provider participation in these registries to obtain important information about fetal abnormalities and dose–effect relationships.

Given the many facets of caring for WWE before, during, and after pregnancy, a collaborative, multidisciplinary approach is needed. The neurologists, obstetricians, primary care doctors, clinical pharmacists, and nurses have key roles in managing epilepsy and complex medication regimens as well as providing effective counseling and education regarding the benefits and risks involved with pregnancy

in WWE. Available resources provide knowledge and tools for effective medication management strategies to care for WWE before, during, and after pregnancy.

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Disclosure

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