Epilepsy in Pregnancy

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KEYWORDS

• Epilepsy • Pregnancy • Contraception • Infertility • Teratogenicity
• Labor and delivery • Breastfeeding

KEY POINTS

- Discussions about contraception and pregnancy with women with epilepsy should occur at every visit.
- Women with epilepsy should contact their provider if they become pregnant and should not stop antiepileptic drugs on their own.
- Clinicians should advise all women of childbearing potential to take at least 0.4 mg of folic acid daily to optimize cognitive outcomes in offspring.
- Valproate should be avoided for women of childbearing potential due to the high risk of teratogenesis. Lamotrigine and levetiracetam are the safest antiseizure medications for pregnancy.
- Breastfeeding should be encouraged for women with epilepsy.

INTRODUCTION

Epilepsy is a prevalent, chronic, and serious neurologic disease for which treatment usually must be maintained during pregnancy. Therefore, the teratogenic risk of antiepileptic drugs (AEDs) is an obvious concern but it is one among many. Most management strategies surrounding pregnancy involve counseling, therefore this article is organized to address the common questions posed by women with epilepsy (WWE) in a naturalistic and chronologic sequence, as would be encountered in an office visit.

CONTRACEPTION

The choice of contraception for WWE is complex due to interactions between enzyme-inducing AEDs (EIAEDs) and hormonal contraceptives. Because about 65%

Disclosure Statement: The authors report no disclosures.
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Neurol Clin 37 (2019) 53–62
https://doi.org/10.1016/j.ncl.2018.09.008
0733-8619/19/

of pregnancies are unplanned, discussion regarding contraception, until when or if pregnancy is sought, should occur at every office visit.[1] Ideally, WWE should be counseled regarding the choice of contraceptive and its interaction with AEDs before they become sexually active. Two major concerns are hormonal contraceptive failure and reduced AED efficacy, both of which are due to pharmacokinetic interactions between these 2 medication types through cytochrome (CYP)P450-P3A4 (CYP3A4).[2]

AEDs with CYP3A4 enzyme-inducing properties, including carbamazepine, oxcarbazepine, felbamate, phenytoin, primidone, topiramate, perampanel, and phenobarbital decrease circulating levels of estrogen and the progestins (synthetic forms of progesterone) in oral contraceptives because these hormones are substrates for CYP3A4.[3] Although clear evidence for oral contraceptive failure with EIAEDs has been scant, a principle-proving study has been performed. In a double-blind, randomized, crossover trial, ovulation rates were much higher during carbamazepine administration compared with placebo in women taking a combined oral contraceptive (COC).[4] These findings can be extrapolated to a potential for contraceptive failure with all EIAEDs. This risk cannot be mitigated by a COC containing a higher dose of estrogen because only the progestin component of the COC provides contraception, primarily via inhibition of ovulation. The low-dose progestin-only formulations may not consistently inhibit ovulation due to the low dose they deliver but may prevent pregnancy through peripheral mechanisms, the most important of which is by thickening cervical mucus and preventing sperm passage.

WWE taking EIAEDS should be advised to use condoms with spermicide, depot medroxyprogesterone injections, or intrauterine devices (**Table 1**). AEDs that have no interactions with hormonal contraceptives and pose no risk of contraceptive failure are valproic acid, vigabatrin, gabapentin, tiagabine, levetiracetam, zonisamide, ethosuximide, and benzodiazepines, including clobazam and clonazepam.[5]

In the other direction of pharmacologic interaction, the estrogenic component of COCs can lower lamotrigine levels by 40% to 60%, increasing the risk of breakthrough seizures. Estradiol induces uridine-diphosphate glucuronosyl transferase (UGT), which catalyzes glucuronidation, the major metabolic pathway for lamotrigine.[6] Therefore, lamotrigine levels should be carefully monitored before and after starting a COC, and doses adjusted accordingly, potentially by up to 50%. Lamotrigine levels are not

Table 1
Choice of contraception

Form of Contraception	Risk of Contraceptive Failure
COC pill (estrogen and progesterone)	Contraceptive efficacy lower with hepatic enzyme-inducing drugs: carbamazepine, oxcarbazepine, felbamate, phenytoin, primidone, topiramate, perampanel, and phenobarbital
Progesterone-only pill	Contraceptive efficacy lower with hepatic enzyme-inducing drugs and likely with lamotrigine
Depot injection	Not affected
Implant	Similar effects to COC
Dermal patch	Similar effects to COC
Vaginal ring	Similar effects to COC
Intrauterine device	Not affected
Mechanical barrier (diaphragm, cup, male or female condom)	Not affected

affected by the progestins of COCs. However, lamotrigine induces the clearance of progestins with a resultant decrease in progestin level of approximately 20%. Therefore, although the progestin-only OC may seem to be reasonable for women taking lamotrigine, the risk of contraceptive failure would predictably be increased with this combination as well.

UGT glucuronidation is also important for valproate and eslicarbazepine metabolism, and COCs clearly reduce valproate levels by 20% to 40%. There is a potential for COCs to also lower eslicarbazepine levels. These latter 2 AED interactions with COCs have not generally been clinically important.

INFERTILITY

Birth rates among WWE are lower than the general population. A Finland registry comprising 12,058 subjects over 39 years, 222 of whom were identified to have epilepsy, found fewer children among adults with active epilepsy.[7] However, low birth rates do not translate directly into infertility. Psychosocial contributors, such as low marriage rates and less desire to have children, are reported in WWE.[8] The direct relationship between epilepsy and infertility remain unclear.

A recent prospective observational trial enrolled WWE who are actively seeking pregnancy. Sexual activity and menstrual cycle were matched to controls, thus eliminating some of the psychosocial factors of low birth rate. In this study, no difference was found between the epilepsy and control group in pregnancy rates (60.7% vs 60.2%, respectively), or median time to pregnancy (6 months vs 9 months, respectively) at 1 year.[9] However, nearly all subjects in this study were taking either lamotrigine or levetiracetam monotherapy, which is important to note when considering the generalizability of this study. Only a few subjects were taking EIAEDs that are known to alter endogenous (as well as exogenous) reproductive hormone levels. Therefore, with the use of EIAEDS, an effect on fertility could be postulated.

Indeed, in a naturalistic observational study, the use of phenobarbital and polytherapy in WWE trying to conceive were risk factors for infertility. In this study, the number of AEDs taken was positively associated with a higher rate of infertility (1 AED 31.8%, 2 AEDs 40.7%, and 3 or more AEDs 60.3%). Use of 3 or more AEDs has an odds ratio as high as 17.9. Half of the women who took phenobarbital were unable to conceive over several years of attempt at conception. Furthermore, the overall association of EIAEDs with infertility risk is supported by the findings.[10]

RISK OF ADVERSE OUTCOMES IN THE MOTHER

Pregnancy does not generally alter the frequency of seizures in WWE. Although percentages vary across studies, in approximately 60% of patients, seizure frequency is similar to that of the prepregnancy baseline, whereas 15% experience an increase in frequency and 15% experience a decrease.[11] If the patient was seizure-free for 1 year before pregnancy, it is very likely (80%) that she will continue to remain seizure-free during pregnancy.[12] Rates of status epilepticus in pregnant WWE are comparable to the annual frequency of 1.6% in the general epilepsy population.[13]

Other maternal pregnancy-related complications, such as gestational hypertension and preeclampsia, may be increased in WWE with an odds ratio of about 1.5, based on a Norwegian population-based registry.[14] AED use contributed to the overall risk.[15] However, no difference in incidence of these complications between WWE and controls was found in a prospective controlled study of 179 pregnancies in WWE.[16]

Therefore, the risk of these complications may be slightly increased but is certainly close to the range of the expected incidence.

Maternal mortality is 10-fold higher in WWE than the general population, most of which is presumably due to sudden unexpected death in epilepsy (SUDEP), which is commonly known by its acronym.[17] In 1 report, half of the epilepsy-related deaths (79% from SUDEP) occurred in patients who were on lamotrigine as monotherapy, highlighting the importance of monitoring drug levels that are affected by hormonal changes (see later discussion).[18]

RISK OF ADVERSE OUTCOMES IN THE FETUS

About 24,000 babies are born to WWE in the United States each year. There is an increased risk of small for gestational age birth weight and head circumference in association with AED use.[19,20] Seizures during pregnancy have not been linked to immediate fetal complications, except in cases of maternal hypoxia, in which fetal bradycardia has been documented, which is reversible with the termination of seizure activity.[21] However, some studies reported an increased risk of preterm birth in women with untreated epilepsy compared with women without epilepsy.[22] This trend is observed in a separate study in a subgroup of WWE who smoke.[23] Therefore, it is especially important to counsel WWE regarding smoking during pregnancy.

The most well-known and documented AED teratogenicity is valproate causing neural tube defects. The risk of valproate causing major congenital malformations (MCMs) is 10% and is clearly dose-associated. Daily doses of 1500 mg per day or greater are associated with a risk of 24%, whereas doses of 700 mg per day or less carry a risk of 5% to 6%.[24] These malformations are serious and consist of midline defects such as spina bifida, hypospadias, and brain malformations in utero, the latter of which may not be compatible with a viable pregnancy. Limb defects such as radial ray malformations also occur. The risk of neural tube defects, cardiac malformations, and facial clefts in general occur at a higher rate with in utero AED exposure and are considered a drug class effect; however, the risk with valproate is significantly higher than with other AEDs. Further, valproate exposure in utero is associated with an increased risk of autism or autism spectrum disorder, even when maternal epilepsy is not present.[25] Consistent with this association, valproate exposure in utero was found to cause reduced cognitive outcomes in children tested at 6 years of age; this risk was also related to dose. In general, the comparator arms of phenytoin, carbamazepine, and lamotrigine in this study were associated with expected cognitive outcomes in exposed offspring. Importantly, in this study, folic acid use of at least 0.4 mg per day and breast-feeding (see later discussion) were both associated with improved cognitive outcomes. The adverse effect of valproate was nearly normalized to the expected range of cognitive scores in the valproate-exposed but breastfed group.[26]

Other important and specific MCMs are cardiac defects with phenobarbital, the first AED found to be teratogenic from the North American AED Pregnancy Registry, with an overall risk of MCMs of 6%, and cardiac defects with topiramate, which carries a risk of 4%, with facial clefts as the specific adverse outcome.[27] With topiramate and zonisamide exposure, there is also a clear risk of low birth weight.[28] Lamotrigine, carbamazepine, phenytoin, and levetiracetam, the other AEDs evaluated in this study, were associated with a teratogenic risk for MCMs between 2% and 3%, rates of which do not clearly differentiate from the risk in the general population.[27] From a recent Cochrane review of this topic, levetiracetam and lamotrigine were found to carry the lowest teratogenic risk.[29] These considerations must be balanced with the risk of seizures also present with their use if the levels decrease to a nonprotective range.

The US Food and Drug Administration (FDA) category of pregnancy risk for AEDs is presented in **Table 2**. While these categories still stand for the AEDs listed, as of June 30th, 2015 the FDA is no longer using these letter categories to denote pregnancy risk. Pregnancy risk for newly approved medications will include a brief discussion of registry information when available, lactation information and available clinical information regarding contraception and infertility. Drugs previously approved will be gradually changed over to the updated presentation of risk.

The risk of the child developing epilepsy in life depends mainly on the type of epilepsy in the mother. Patients with hereditary epilepsy syndromes should be counseled accordingly. An increased incidence of epilepsy is associated with decreasing gestational age and birth weight. Children born at 22 to 32 weeks with a birth weight of less than 2000 g have a 5-fold increase in risk of developing epilepsy in the first year of life compared with children born 39 to 41 weeks with birth weight of 3000 to 3999 g.[30]

PRACTICAL MANAGEMENT OF ANTIEPILEPTIC DRUGS

WWE should discuss plans of pregnancy with their health care provider, and providers should be open to each individual's choice regarding risks and benefits of AEDs. However, clinicians should communicate 1 clear message to their patients: if they discover they are pregnant, do not stop taking AEDs and call their provider to discuss next steps in management. Pregnant WWE are twice as likely to stop AED as nonpregnant WWE[31] and it is a fundamental principle of care that uncontrolled epilepsy poses a major health risk to the mother as well as the fetus.

Before conception, seizure control should be optimized because seizure frequency in the previous year is comparable to that of pregnancy.[31] However, this predictor depends on the AED level not decreasing more than 35% of the preconception level, which may be challenging due to changes in pregnancy such as increased drug clearance, volume expansion, and hormone fluctuations.[32] The American Academy of Neurology (AAN) recommends monitoring AED levels during pregnancy.[33] Therefore, it is important to first establish a therapeutic range in the preconception stage to

Table 2
US Food and Drug Administration pregnancy categories of antiepileptic drugs

FDA Category C drugs	FDA Category D drugs
• Acetazolamide	• Carbamazepine
• Clobazam	• Clonazepam
• Ethosuximide	• Phenobarbital
• Felbamate	• Phenytoin
• Gabapentin	• Topiramate
• Lamotrigine	• Valproate
• Levetiracetam	
• Oxcarbazepine	
• Tiagabine	
• Vigabatrin	
• Zonisamide	

FDA category 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. FDA category 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. There are currently no FDA Category A or B AEDs.

eliminate interindividual variations. Levels may be checked in each trimester and in the postpartum period.[34] Lamotrigine and oxcarbazepine levels should be followed more closely, at monthly intervals or even more frequently, owing to their marked increase in clearance in the setting of high estrogen levels. Levetiracetam and zonisamide also decrease markedly during pregnancy owing to increased renal clearance, and should be followed closely.

In patients with controlled epilepsy, attempts should be made to reduce the AED dose to the lowest therapeutic range during preconception. Polytherapy should also be avoided because it likely increases the risk of MCMs.[35] In the UK Epilepsy and Pregnancy Registry of 3607 cases, the risk of malformations with polytherapy is 6.0%, as opposed to 3.7% with monotherapy.[36] The risk is especially higher with the use of valproate.[37]

The AAN and Epilepsy Foundation encourage all WWE to take folic acid supplementation, possibly at a higher dose (4 mg) than what is recommended for the general population (0.4 mg).[33,38] Folic acid is a B vitamin involved in the synthesis of purines, which are required for DNA formation, and low levels are associated with reduced growth and anemia. Infants of women on folic acid antagonists (dihydrofolate reductase inhibitors), such as phenytoin, phenobarbital, or carbamazepine, during the first trimester are at higher risk of MCMs with a relative risk of 3.4.[39] Folic acid deficiency has also been implicated in neural tube defects in the general population, which is a known adverse outcome with the use of valproate and carbamazepine during pregnancy.[40] Finally, WWE on hepatic EIAEDs are at increased risk of low folic acid by up to 90%.[41] Therefore, although there are no randomized controlled trials studying the effects of folic acid in preventing MCMs in WWE, the protective effect of folic acid supplementation on cognitive outcome has been shown.[26] Therefore, all WWE should be encouraged to take at least 0.4 mg of folic acid daily.

LABOR AND DELIVERY

Seizures during delivery occur in about 2% of WWE,[42] with greater risk to those who have subtherapeutic AED levels.[43] Maternal seizures in labor may result in prolonged uterine contractions with slowing of fetal heart rate.[44] A Swedish study of 1,429,652 births, 5373 of which were births to 3586 WWE, showed that WWE are at risk of adverse delivery outcomes, including peripartum infection, placental abruption, induction, and elective cesarean section, after adjusting for psychosocial confounders.[45] Similarly, in a US study of 20,449,532 delivery hospitalizations, 69,385 of which were of WWE, there is a higher risk of preeclampsia, preterm labor, increased cesarean delivery, and prolonged hospital stay (>6 days), as well as a 10-fold increased risk of mortality (adjusted odds ratio 11.46).[46] Thus, although epilepsy is not an indication for cesarean delivery, home births are highly discouraged. WWE are recommended to deliver in a hospital setting and take their AEDs regularly through labor.

BREASTFEEDING

Breastfeeding provides many benefits for the infant, including nutrition and immunoprotection, as well as social development. Most concerns with breastfeeding lie in the potential transfer of AEDs through breast milk and their side effects. However, few studies have established minimal, if any, disadvantage to breastfeeding in women with treated epilepsy. Continuous breastfeeding in the first 6 months of life is associated with improved outcome in fine motor, gross motor, and social skills in a Norwegian Mother and Child Cohort Study (n = 78,744).[47] In another study of 181 children with mothers on AED monotherapy, in which approximately half of the children were

Table 3
Counseling

Stage	
All women diagnosed with epilepsy • I have a boyfriend and I am sexually active; what do I need to know or do? • What kind of birth control should I use? • I am planning to have children in the future. What should I do?	• Ask if the patient is sexually active. Supplement folic acid. • Depending on the AED, the patient's contraception options should be discussed. • Encourage the patient to discuss family planning with the provider in advance and to run all medication changes by the provider.
Preconception • Will I have trouble getting pregnant? • How do I adjust my medicine before pregnancy? Can I come off my medicines? • What vitamins do I need to take? • What tests do I need to take?	• Reassure the patient that fertility is the same as the general population in WWE actively seeking to become pregnant. • Optimize seizure control and AED regimen. Use as few AEDs at as low doses as possible. Patients with uncontrolled epilepsy should not discontinue their AEDs. • Supplement folic acid if not already taking. • Establish therapeutic AED levels.
Pregnancy • Will my seizures increase? • What should I do if I have a seizure? • Does having a seizure affect my baby? • How is my seizure medicine going to affect my baby? • Do I need to have a cesarean section? • Can I have a home birth?	• Reassure patient that seizure frequency is usually similar to preconception. • General seizure management remains the same. AED levels should be checked at least each trimester. If a patient has a breakthrough seizure, try to identify triggers, such as decreased absorption of AEDs due to hyperemesis gravidarum. Discuss dose increase or addition of AEDs with patient based on risks and benefits. • There is little evidence to suggest that seizures per se in the mother adversely affect the fetus except in prolonged seizures or with direct trauma. • MCMs are rare but more common than the general population. Risks and benefits of AED treatment should be discussed with the patient and the decision made based on her preference. • Epilepsy is not an indication for a cesarean section but the obstetrician should be aware of the diagnosis and be prepared. • Home birth should be discouraged due to potential seizures during labor.
Postpartum and breastfeeding • Can I breastfeed? • Can I hold the baby? • Will I need help to take care of my newborn baby?	• Encourage patient to breastfeed. • In patients with uncontrolled epilepsy, a safety strap is recommended while holding the baby. • WWE should obtain as much help as frequently as they can to promote adequate self-care, including sleep, stress reduction, and mood.

breastfed for a mean of 7.2 months, breastfed children exhibited higher IQ at 6 years of age, with no observed side effects.[48] Breastfeeding also reduces the risk of the child developing epilepsy at 1 year of age in a dose-dependent fashion; children who were breastfed longer had decreasing risk.[49] WWE should be reassured and encouraged to breastfeed.

In considering AEDs, lipophilic drugs have a high penetrance into breast milk, whereas protein-bound drugs have lower penetrance. Phenytoin, valproate, and carbamazepine are moderately to highly protein-bound and have a low milk to plasma ratio.[50] Very few case reports of adverse reaction are documented.[51] Most other AEDs have either a low penetrance into breast milk, low infant serum drug levels, or rare side effects. Two exceptions are phenobarbital and benzodiazepines. Due to their long half-lives (diazepam has a half-life of 30 hours in newborns), drugs can accumulate, causing drowsiness and poor weight gain. Careful monitoring is warranted.[50]

Counseling strategies based on common questions posed by patients and families are presented in **Table 3**.

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