

BRIEF REPORT

Caring for Women with Epilepsy: A Brief Review

Ananya Vasudhar, MBBS¹, Sukriye Damla Kara, MD¹

¹ Neurology, University of Mississippi Medical Center

Keywords: Epilepsy, women, female, pregnancy, postpartum

<https://doi.org/10.67225/001c.119014>

Journal of the Mississippi State Medical Association

Vol. 65, Issue 5/6, 2024

Epilepsy is a neurological disorder that affects approximately 3 million adults in the United States. There are unique considerations and challenges in caring for women with epilepsy. This brief review aims to highlight key points of epilepsy care tailored to women, including hormonal influences in epilepsy, contraception, prepartum considerations, antiseizure medication safety in pregnancy, and postpartum care.

Introduction

Epilepsy is a neurological disorder that affects approximately 3 million adults in the United States.¹ There are unique considerations and challenges in caring for women with epilepsy. This brief review aims to highlight key points of epilepsy care tailored to women, including hormonal influences in epilepsy, contraception, prepartum considerations, antiseizure medication safety in pregnancy, and postpartum care.

Hormonal Influences on Epilepsy

Studies have shown that there is an intricate bidirectional relationship between seizures and female sex hormones. Estrogen exhibits proconvulsant effects as a result of its excitatory properties. Its main mechanism of action involves promoting kindling and increasing the activity of glutamate receptors, ultimately leading to a reduction in the seizure threshold. Progesterone, on the other hand, is anticonvulsant, and it increases postsynaptic GABA activity.²

Animal studies have shown close anatomical interrelations between the temporolimbic system and the hypothalamic-pituitary-adrenal axis. As a result of this interdependence, women with epilepsy are shown to have a higher rate of menstrual irregularities, polycystic ovaries, amenorrhea, and premature menopause.³

Antiseizure medications can cause hormonal dysregulation, as they may decrease levels of free sex steroid hormones by inducing hepatic metabolism and increasing the production of sex hormone binding globulin.⁴

Catamenial Epilepsy

Catamenial epilepsy is defined by the cyclical seizure exacerbation with a temporal relationship to the menstrual cycle. Hormonal influences of estrogen over progesterone during the pre-ovulatory phase of the menstrual cycle are associated with seizure exacerbation. In women experiencing anovulatory cycles, there is an elevation in estrogen levels observed between day 14 and menstruation, along with insufficient levels of luteal progesterone.⁵

The treatment of catamenial epilepsy has been the subject of several studies. The available treatment modalities depend on whether a woman has regular or irregular menstrual periods. Treatment options for women with regular menstrual cycles include clobazam, acetazolamide, or adjusting the dosage of one antiseizure medication during the anticipated period of heightened risk. Contraceptive methods, such as the administration of medroxyprogesterone (Depo-Provera) or gonadotropin-releasing hormones like Triptorelin and goserelin, may be used to suppress menstruation in women experiencing irregular menstrual cycles.⁶

Gender-affirming hormone therapy

It is important to consider hormonal factors in treatment of epilepsy. Transgender patients with epilepsy may experience discrimination and be reluctant to discuss their gender identity with healthcare providers, ultimately leading to inappropriate choice of antiseizure medications. Valproate can be associated with masculinizing aesthetic side effects such as alopecia, hirsutism and weight gain. Gender-affirming medications and antiseizure medications may interact with each other in a bi-directional way. Lamotrigine levels may be decreased in patients taking oral 17-beta-estradiol. Enzyme-inducing antiseizure medications can lower gonadotropin-releasing hormone analog, medroxyprogesterone, 17beta-estradiol, transdermal estrogen and spironolactone.⁷

Contraception

Counseling women with epilepsy on family planning, contraception, and the impact of seizures and anti-seizure medications on pregnancy is a crucial component of their care. Women with epilepsy are often unaware of the interactions between enzyme-inducing anti-seizure medications and hormonal contraceptives, which increases the risk of contraceptive failure and unplanned pregnancies.⁸

Approximately 50% of pregnancies are unplanned; additionally, women may only realize they're pregnant around 6.5 weeks, after the critical neural tube closure at 4 weeks. This timing poses a greater risk for women with epilepsy who are taking enzyme-inducing antiseizure medications, which are linked to structural teratogenicity.⁴ According to a study published using

data from The Epilepsy Birth Control Registry, women with epilepsy have a 6.75-fold higher likelihood of experiencing seizures when using hormonal contraception compared to those who used barrier methods.⁹

When considering contraceptive choices for women with epilepsy, it is important to consider their effectiveness in preventing unintended pregnancies, their potential interactions with hormones and antiseizure medication, as well as any hurdles that may hinder their usage of medication. Contraceptives are broadly divided into hormonal and non-hormonal. Among hormonal contraceptives are oral combined contraceptive pills, dermal patches, and vaginal rings, which should be avoided with enzyme-inducing antiseizure medications. An important consideration to make while using estrogen-based birth control is that they can lower the serum levels of lamotrigine by 50%, potentially leading to breakthrough seizures. The efficacy of progesterone-based contraceptives such as progestin-only pills, implants, and depot medroxyprogesterone acetate injections, may be reduced by enzyme-inducing antiseizure medications. Progesterone-only intrauterine device (IUD) is considered the most reliable contraceptive method with a low rate of unintended pregnancies at 0.1%. Since it has a localized mechanism, it does not impact the serum concentrations of antiseizure medications. Furthermore, antiseizure medications do not affect the efficacy of intrauterine devices. Non-hormonal contraceptives, including Copper or steel intrauterine devices with an unplanned pregnancy rate of 0.8%, and permanent methods like vasectomy and tubal ligation with rates of 0.15% and 0.5% respectively, are effective options that do not impact antiseizure medications, and vice versa.^{4,10}

Epilepsy in pregnancy

Prenatal care

The objective of prenatal counseling is to optimize pregnancy planning, mitigate the likelihood of seizure recurrence, and limit the adverse effects of antiseizure medications on the mother and fetus. Physiological changes that occur during pregnancy, such as an increase in plasma volume, a reduction in serum albumin levels due to hemodilution, and changes in hepatic drug metabolism, can lead to a decrease in serum levels of anti-seizure medications such as lamotrigine and levetiracetam.¹¹ Studies have shown that decrease in the serum concentrations of antiseizure medications, requiring polytherapy for seizure control, and the seizure frequency prior to conception are some indicators that can predict the occurrence of seizures during pregnancy.¹²

According to results from the recent Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study, pregnant women with epilepsy required more frequent dose adjustments of antiseizure medication compared to the nonpregnant cohort - which emphasizes the need for close dose monitoring during pregnancy.¹³ It is

crucial to optimize the drug regimen prior to conception in order to provide effective seizure control. This effectiveness can be achieved by modifying the regimen from polytherapy to monotherapy or by reducing the dosage of medication if monotherapy is being used.

It is advised for all women of childbearing age with epilepsy to take folic acid supplementation of 0.4mg daily.¹⁴ While there is limited data on the recommended folic acid dosage for women with epilepsy, current guidelines suggest taking 0.4 mg to 5 mg of folic acid daily, starting at least 3 months before planning to conceive. Higher doses are recommended for women with increased risk, such as those taking high doses of valproate, polytherapy with valproate and topiramate, and women with a personal or family history or prior pregnancy with a major congenital malformation.^{4,15}

Genetic testing in Epilepsy

Women with epilepsy who are planning pregnancy often have concerns about the potential impact of epilepsy and anti-seizure medications on the developing fetus, as well as the likelihood of their child developing epilepsy.

The risk of the child developing epilepsy, both generalized and focal, is increased compared to the baseline. Standard preconception genetic testing and carrier screening usually do not include genetic counseling and testing for epilepsy. When providing preconception counseling to patients with epilepsy, it is crucial to consider causes of epilepsy and whether patients have an epileptic syndrome that could affect their future child.

We also recommend considering genetic counseling for patients with first-degree relatives with epilepsy.¹⁶

Fertility and assisted reproductive technology

In a 2018 observational prospective study, the objective was to determine if there was any difference between women with epilepsy, who do not have a pre-existing diagnosis of infertility or associated disorders, and women without epilepsy when attempting to become pregnant; it was concluded that both groups had comparable changes of conceiving and live birth rates.¹⁷

Treating women with epilepsy undergoing reproductive treatments requires special attention because the hormonal effects of these therapies may have a bidirectional influence on seizure control and antiseizure medications.¹⁸ However, it is reassuring that the chances of successful assisted reproductive technology treatment for women with epilepsy are similar to those for women without epilepsy.¹⁹ Although there are no current guidelines, we recommend monitoring levels of anti-seizure medications, particularly enzyme-inducing antiseizure medications, such as lamotrigine during these fertility treatments.

During pregnancy

Convulsive seizures pose a threat to both the mother and the developing fetus: potential to cause hypoxemia, particularly when it persists for an extended period. Additionally, these seizures increase the likelihood of falls and blunt trauma. There is a lack of substantial data indicating a direct causal relationship between maternal seizures and congenital abnormalities.

In the general population, 2.2% of babies born to pregnant women without epilepsy who are not on antiseizure medication will have a congenital malformation. This risk increases to 6.1% for pregnant patients with epilepsy treated with antiseizure medications. The risk is still slightly higher (2.8%) for women with epilepsy not taking any antiseizure medications; however, there is additional fatal risk to both mother and baby due to trauma, premature labor, and miscarriage from uncontrolled seizures. Seizure control is of utmost importance during pregnancy, as the risks of uncontrolled seizures outweigh the risks from medications. The risk from medications can be further reduced by choosing low-risk profile anti-seizure medications.²⁰

Various anti-seizure medication pregnancy registries have now been established, and one of the most important findings has been that in-utero exposure to valproate is associated with a higher risk of congenital abnormalities compared to other anti-seizure medications. Many anti-seizure medications have been shown to have a dose dependent risk for teratogenicity. These risks have shown to be higher during exposure in first trimester.

Based on studies, valproate has the highest risk for anatomical malformations, while phenytoin, phenobarbital, and topiramate have intermediate risk. Carbamazepine, oxcarbazepine, lamotrigine, and levetiracetam has been shown to have the least documented risk.²¹ Currently there is insufficient data on safety profile of combinations of polytherapy.

Exposure to anti-seizure medications has also been linked to cognitive and behavioral impairment. Multiple studies have investigated the neurodevelopmental outcomes of fetal exposure to anti-seizure medications. Data from the Neurodevelopmental Effects of Anti-seizure Drugs (NEAD) study on women with epilepsy on monotherapy showed lower IQ in children with in-utero exposure to valproate compared to children of women treated with carbamazepine, lamotrigine or phenytoin.²² Studies have also shown an increased risk for autism spectrum disorder and attention deficit hyperactivity disorder (ADHD) in children exposed to valproate.²³

Normal metabolic changes in pregnancy impact the pharmacokinetics of antiseizure medications. The fluctuations in serum levels of antiepileptic drugs are contingent upon individual metabolic activity, the specific type of anti-seizure medication, and the patient's unique responsiveness to drug dosage.²⁴ During pregnancy, the serum concentrations of certain medicines,

such as lamotrigine, are greatly affected due to variables including drug clearance, resulting in a major decrease. However, other drugs like carbamazepine do not have significant changes in levels during pregnancy. Anti-seizure medication level at which seizure control is achieved should be established at baseline, which helps to establish the patient's optimal serum concentrations. Currently, there is no standardized protocol for monitoring the levels of anti-seizure medications in pregnant women with epilepsy. However, it is fair to consider monthly monitoring of drug levels for anti-seizure medications that are known to have fluctuating serum concentrations.²⁵ Caution must be exercised while making dose modifications during pregnancy, and it is crucial to be aware that these concentrations can rapidly revert as early as one to three days after giving birth.

Pregnant patients with epilepsy should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry. Providers can access the latest study data on the prevalence of major malformations for antiseizure medications by accessing aedpregnantregistry.org.

Postpartum care

The postpartum period is particularly challenging for mothers with epilepsy. An increase in seizure frequency may be seen in patients during postpartum period due to sleep deprivation, missed medication, and increased stress. Consequently, it is essential to address sleep hygiene and provide guidance to patients and their families on techniques that ensure uninterrupted and regular nightly sleep. Having a comprehensive discussion and placing a strong emphasis on safety precautions is crucial during the postpartum period. These precautions consist of refraining from driving, avoiding bathing the infant without the presence of another individual, and avoiding co-sleeping with the newborn in the same bed.

A recent prospective trial revealed that pregnant women with epilepsy experienced more severe symptoms of depression and anxiety during pregnancy and postpartum compared to non-pregnant women with epilepsy and healthy pregnant women, although the overall incidence of major depressive episodes was similar between the groups.²⁶ We recommend that more frequent screening for mood disorders should be considered in pregnant women with epilepsy.

Antiseizure medication levels should be obtained after delivery to adjust dosing for safety measures. Lamotrigine levels should be measured sooner-1-2 weeks postpartum to ensure safe maternal levels with dose adjustments-and repeated levels should be obtained until safe levels are re-established.

Breastfeeding

The prevalence of breastfeeding has been observed to be comparatively lower in women with epilepsy, potentially due to the concern regarding the transmission of antiseizure medications through breastmilk.¹⁵ Studies have shown that lamotrigine, levetiracetam, topiramate, and gabapentin may accumulate in breastmilk in potentially clinically significant amounts, whereas very low concentrations of valproate, phenytoin, and carbamazepine were reported.²⁷ Women with epilepsy on barbiturates and lacosamide should be advised to monitor their newborn for poor feeding or increased sleepiness.²⁸

Mothers with epilepsy may be hesitant to breastfeed their children as they may be concerned that antiseizure medication exposure via breast milk may have adverse effects on their children's development. However, a prospective observational multicentre study showed no adverse effects of antiseizure medication exposure via breast milk at 6 years of age, and breastfed children had higher IQs and better verbal skills.²⁹ Breastfeeding is a crucial aspect of the postpartum period for both the mother and the newborn, and it is imperative to promote breastfeeding among women with epilepsy, regardless of the use of antiseizure medication use.

Conclusion

Caring for women with epilepsy requires a nuanced approach with special awareness of hormonal factors that influence seizure control and anti-seizure medications. Early initiation of pregnancy planning and contraception counseling is recommended for women with epilepsy who are of childbearing age. This early consideration allows for the timely initiation of folic acid supplements and ensures awareness of potential interactions. Anti-seizure medication level at which seizure control is achieved should be established at baseline, ideally prior to pregnancy; establishing this helps to determine the patient's optimal serum concentrations as the alterations in serum concentrations differ across individuals. Special populations in epilepsy, such as postpartum patients, menopausal patients, and transgender patients on gender-affirming hormone therapy may have special considerations and needs in epilepsy treatment. The bi-directional play between hormones and anti-seizure medications should be kept in mind when choosing treatment, and appropriate monitoring of antiseizure medication levels should be done timely.

Submitted: March 27, 2024 CDT. Accepted: May 16, 2024 CDT. Published: June 11, 2024 CDT.

Anti-seizure medication	Mechanism of action ^a	Maximum dose	Decrease in serum concentrations*	Recommendation to monitor drug levels [#]	Interaction with contraception or effect on hormones	Adverse effects	Teratogenicity and lactation ^b
Carbamazepine	Binds to voltage-dependent sodium channels and inhibits the generation of rapid action potentials	1600 mg/day	0-12% ^c	Optional	Strong inducer	Stevens-Johnson syndrome, toxic epidermal necrolysis and bone marrow suppression; need to screen pts of genetically at-risk ancestry for HLA-B1502 allele before tx initiation	Neural tube defects, craniofacial defects, cardiovascular malformations Monitor breastfeeding infant, low risk of thrombocytopenia (limited human data)
Clobazam	Binds to the GABA(A) receptor and increase the neuronal membrane permeability to chloride ions	40 mg/day	Limited data**	Optional	Weak inducer	Somnolence, constipation	Risk of neonatal respiratory depression, hypotonia, sedation and withdrawal seizures Possible risk of infant CNS depression (limited human data on breastfeeding)
Lacosamide	Enhances slow inactivation of voltage-dependant sodium channels which leads to stabilisation of neuronal membrane and inhibition of repetitive neuronal firing	400 mg/day	Up to 39.9% ^d	Yes	Non-inducer	Dizziness, nausea, abnormal coordination	No known risk of teratogenicity Possible risk of infant sedation with breastfeeding
Lamotrigine	Although not completely understood, it has been shown to block the repetitive firing of neurons by inactivating voltage dependent sodium channels	400-600 mg per day	17-69% ^c	Yes	Weak inducer	Severe rash, Steven Johnson syndrome, depression exacerbation among others	Dose adjustment may be needed during pregnancy and postpartum (risk of decreased maternal drug levels during pregnancy) Conflicting human data on possible risk of teratogenicity Consider monitoring infant lamotrigine levels during breast feeding Low risk of infant harm

Anti-seizure medication	Mechanism of action ^a	Maximum dose	Decrease in serum concentrations*	Recommendation to monitor drug levels [#]	Interaction with contraception or effect on hormones	Adverse effects	Teratogenicity and lactation ^b
Levetiracetam	Exact mechanism is unknown, shown to bind to the synaptic vesicle which may modulate synaptic transmission through alteration i=of vesicle fusion	4000 mg per day	40-60% ^c	Yes	Non-inducer	Fatigue, somnolence	Dose adjustment may be needed during pregnancy and postpartum (risk of decreased maternal drug levels during pregnancy) Risk of teratogenicity not expected, however there is possible risk of intrauterine growth restriction (limited human data) No known risk of infant harm during breastfeeding (limited data)
Oxcarbazepine	Block voltage-sensitive sodium channels and modulate the activity of high-voltage activated calcium channels	2400 mg per day	Up to 32.6 % ^d	Yes	Strong inducer	Sedation, headache, dizziness, rash	Conflicting human data on possible risk of teratogenicity Inadequate human data on risk of breastfeeding
Perampanel	AMPA-type glutamate receptor antagonist and reduces neuronal excitability	12 mg per day	Limited data **	Yes	Strong inducer	Dizziness, somnolence, irritability, alteration of mood ad aggression	No human data available on pregnancy No human data available for breastfeeding
Phenobarbital	Binds to GABA (A) receptor and causes neuronal hyperpolarization	200 mg/ day	Up to 55% ^c	Yes	Strong inducer	Sedation, mood changes including depression	Risk of teratogenicity and neonatal respiratory depression, lethargy, hypotonia, withdrawal seizures, vitamin K deficiency-associated bleeding Risk of CNS depression and withdrawal seizures if abrupt cessation of breastfeeding

Anti-seizure medication	Mechanism of action ^a	Maximum dose	Decrease in serum concentrations*	Recommendation to monitor drug levels [#]	Interaction with contraception or effect on hormones	Adverse effects	Teratogenicity and lactation ^b
Phenytoin	Blocks voltage-dependent neuronal sodium channels	600 mg per day	60-70% ^c	Yes	Strong inducer	Gingival hypertrophy, rash, folic acid depletion	Risk of teratogenicity and neonatal vitamin K deficiency-associated bleeding Monitor breastfeeding infant closely, low risk of methemoglobinemia (limited human data)
Primidone	Binds to the GABA(A) receptor and extends the duration of the GABA-mediated chloride channel openings	2 g per day	Limited data**	Yes	Strong inducer	Sedation, impaired concentration, mood changes	Risk of teratogenicity and neonatal vitamin K deficiency-associated bleeding Risk of infant CNS depression during breastfeeding (limited human data)
Topiramate	Blocks voltage-dependent sodium channels, enhances activity of GABA and antagonises AMPA/kainate-type glutamate receptors	400 mg per day	Up to 30% ^c	Yes	Weak inducer	Cognitive impairment, weight loss, sedation, mood changes including depression	Risk of teratogenicity, oral clefts and low birth weight Inadequate human data on risk of infant harm during breastfeeding
Valproate	Blocks voltage-dependent sodium channels and suppresses high frequency, repetitive neuronal firing	60 mg/kg/day	Up to 23% ^c	Optional	Non-inducer	Nausea, weight gain, teratogenicity, hepatic impairment	Neural tube defects, decreased IQ scores, and neurodevelopmental disorders Monitor breastfeeding infant closely, low risk of thrombocytopenia based on limited data
Zonisamide	Blocks both voltage-dependent sodium and T-type calcium channels	600 mg per day	Up to 35%, limited data ^c	Yes	Non-inducer	Somnolence, ataxia, confusion, fatigue	Low risk of teratogenicity (limited human data), dose adjustment may be needed during pregnancy and postpartum

Anti-seizure medication	Mechanism of action ^a	Maximum dose	Decrease in serum concentrations*	Recommendation to monitor drug levels [#]	Interaction with contraception or effect on hormones	Adverse effects	Teratogenicity and lactation ^b
							Inadequate human data on risk of infant harm during breastfeeding

*Decrease in serum concentrations observed in pregnancy if no dose changes are made.

**To the best of our knowledge limited data exists with respect to alterations of serum concentrations during pregnancy.

[#]We recommend monitoring drug levels during pregnancy and postpartum, if available.

^aSchachter SC. Antiseizure medications: Mechanism of action, pharmacology, and adverse effects. In: uptodate, Connor RF (Ed), Wolters Kluwer. (Accessed on March 8, 2024)

^bEpocrates. (2024). Epocrates medical references. (Accessed March 8, 2024) (version 18.12)

^cTomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epileptic Disord.* 2019;21(6):497-517.

^dAvachat C, Barry JM, Lyu X, Sherwin CM, Birnbaum AK. Management of Anti-Seizure Medications during Pregnancy: Advancements in The Past Decade. *Pharmaceutics.* 2022;14(12):2733. Published 2022Dec 6.

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