REVIEW ARTICLE

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Sexual and Reproductive Health in the Management of Epilepsy

By Meriem K. Bensalem-Owen, MD

ABSTRACT

OBJECTIVE: **The management of epilepsy should be patient centered, and the treating team should carefully balance eliminating seizures while minimizing adverse effects associated with antiseizure medications. This article highlights important aspects of care related to sexual and reproductive health in people with epilepsy.**

LATEST DEVELOPMENTS: **Gender- and sex-based management in epilepsy can present unique challenges especially in people with epilepsy of childbearing potential. One of the most important considerations with the prescription of antiseizure medications to people of childbearing potential involves reproductive health. Folic acid supplementation is recommended to reduce the risk of congenital malformations, but there is no consensus on the optimal dose. The clinical management of pregnancy in the setting of epilepsy can be challenging. Significant knowledge gaps remain regarding the risks for most new antiseizure medications, neurostimulation therapy, and ketogenic diets during pregnancy. Ongoing multicenter pregnancy registries continue to inform practitioners on the medical treatment of people with epilepsy of childbearing potential. Data evaluating the effect of antiseizure medications on male patients with epilepsy, especially around conception, continue to be insufficient.**

ESSENTIAL POINTS: **The decision to prescribe an antiseizure medication depends on several considerations because of the potential for lifetime treatment with a daily medication. It is important to tailor management to the patient's specific circumstances. Seizures and antiseizure medications can both affect sexual and reproductive health. Furthermore, hormone fluctuations may affect seizure frequency, treatment, and contraception. All these factors should be considered when treating people with epilepsy during their reproductive years. In addition, it is important to foster a multidisciplinary approach for the treatment of people with epilepsy.**

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Address correspondence to Dr Meriem K. Bensalem-Owen, Department of Neurology, Kentucky Clinic, 740 South Limestone, Lexington, KY 40536, mkbens2@email.uky.edu.

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INTRODUCTION

Epilepsy is one of the most common neurologic disorders. There are more than 50 million individuals with epilepsy worldwide and 3.4 million in the United States alone.[1] The effects of antiseizure medications and other treatments as well as seizures on sexual and reproductive health should be considered. Hormone fluctuations may also affect seizure frequency, treatment, and contraception. Approximately 12.5 million people of childbearing potential worldwide have epilepsy, more than 1.5 million people with epilepsy of childbearing potential live in the United States, and approximately 24,000 people with epilepsy give birth each year.[2] Pregnancy planning is an essential aspect of caring for people with epilepsy of childbearing potential to minimize and potentially mitigate adverse neurodevelopmental outcomes and major congenital malformations. There are very few studies evaluating the effect of antiseizure medications on male patients with epilepsy and their offspring when antiseizure medications are taken at the time of conception. There are even fewer studies of patients with epilepsy who are lesbian, gay, bisexual, transgender, queer or questioning, intersex, and more (LGBTQI+). Transgender people living with epilepsy have specific health care needs especially when undergoing gender-affirming treatments. The care of people with epilepsy should take into consideration all these factors, frequently requiring a multidisciplinary approach. This article provides up-to-date information to guide practitioners on sexual and reproductive health considerations in the treatment of people with epilepsy.

SEXUAL HEALTH

Healthy sexual function is important to quality of life. The potential effect of epilepsy and its treatments on sexual function is often neglected.

General Sexual Health Considerations

Sexual and reproductive health counseling for people with epilepsy should begin during adolescence and be included in the transition from pediatric to adult health care. It is estimated that sexual dysfunction occurs up to 4 times more frequently in people with epilepsy compared with people who do not have epilepsy.[3] In people with epilepsy, seizures and interictal epileptiform discharges can affect the hypothalamic-pituitary axis as well as the production of gonadal steroids.[4] Enzyme-inducing antiseizure medications can cause sexual dysfunction by affecting the metabolism of gonadal steroids, whereas newer antiseizure medications may affect sexual function through different pathways (TABLE 9-1). Limited evidence suggests that sexual function improves in patients who become seizure free following epilepsy surgery.[4] In a survey of people with epilepsy and their neurologists, the most frequently reported sexual dysfunction included decreased sexual desire, orgasm problems, erection difficulties, and vaginal dryness.[5] In men, studies are limited to only a few antiseizure medications and have mostly evaluated spermatic function. In a study investigating men with epilepsy taking carbamazepine or valproate monotherapy, semen analysis, including volume and number of sperm of normal morphology, were found to be significantly decreased compared with the control group.[6] In addition, there was a statistically significant decrease in free testosterone levels in men taking valproate. A prospective study found that 36.7%

KEY POINTS

- Pregnancy planning is an essential aspect of caring for people with epilepsy of childbearing potential to minimize and potentially mitigate any adverse neurodevelopmental outcomes and major congenital malformations.
- Transgender people living with epilepsy have specific health care needs especially when undergoing gender-affirming treatments.
- Sexual and reproductive health counseling for people with epilepsy should begin during adolescence and be included in the transition from pediatric to adult health care.
- Enzyme-inducing antiseizure medication can cause sexual dysfunction by affecting the metabolism of gonadal steroids, whereas newer antiseizure medications may affect sexual function through different pathways.
- In a survey of people with epilepsy and their neurologists, the most frequently reported sexual dysfunction included decreased sexual desire, orgasm problems, erection difficulties, and vaginal dryness.
- Anorgasmia has been noted with traditional antiseizure medications such as carbamazepine, phenytoin, and phenobarbital as well as with newer antiseizure medications such as topiramate, oxcarbazepine, zonisamide, gabapentin, and pregabalin.

of men with epilepsy have sexual dysfunction.[7] A survey that included 110 men with epilepsy found that they were 3 times more likely to have erectile function issues than men who do not have epilepsy; however, there was no difference in libido.[7] In this survey the most frequently used antiseizure medication was levetiracetam followed by lamotrigine. Phenytoin was the third most used antiseizure medication.

Although most cases of anorgasmia are thought to be related to psychological issues or due to comorbid medical conditions, sexual side effects and anorgasmia with the use of antiseizure medications have been reported. Anorgasmia was noted with traditional antiseizure medications such as carbamazepine, phenytoin, and phenobarbital as well as with newer antiseizure medications such as topiramate, oxcarbazepine, zonisamide, gabapentin, and pregabalin.[8-10] Valproate and enzyme-inducing antiseizure medications may decrease libido. Limited data indicate that newer antiseizure medications, including levetiracetam, lamotrigine, and oxcarbazepine, cause no or minimal sexual dysfunction, whereas some reports showed they may be associated with improved sexual function.[11] A systematic review of 17 studies, mostly case reports and small case series, revealed that topiramate caused sexual dysfunction in up to 12.5% of patients.[12] Female patients mainly had anorgasmia, whereas male patients principally had erectile dysfunction. The patients' symptoms subsided after topiramate was replaced or discontinued. One study found that women with mostly drug-resistant epilepsy asked for help with their sexual problems significantly more often than women in the other groups.[13] People with epilepsy of childbearing potential may develop polycystic ovary syndrome, anovulatory cycles, and menstrual disorders, which seem to be associated with seizure type and frequency and epilepsy duration.[14]

Current data regarding sexual function highlights the need for open discussion between patients and their health care team. The treatment of sexual dysfunction in people with epilepsy may require changing antiseizure medication.

TABLE 9-1 **Commonly Prescribed Enzyme-inducing Antiseizure Medications**

- Carbamazepine
- Clobazam
- Eslicarbazepine
- Felbamate
- Oxcarbazepine (1500 mg/d or more)
- Perampanel (8 mg/d or more)
- Phenobarbital
- Phenytoin
- Primidone
- Rufinamide
- Topiramate (200 mg/d or more)

Patients From the LGBTQI+ Community

Patients living with epilepsy come from diverse backgrounds and may face unique challenges and disparities in care. In addition to the stigma associated with epilepsy, people from the LGBTQI+ community with epilepsy are burdened with social rejection, decreased social support, and discrimination. Official estimates indicate that 7.6 % of the United States population identify as LGBTQI+ and that slightly less than 1% of the population identify as transgender.[15]

LGBTQI+ encompasses people who do not identify as heterosexual or cisgender and this term continues to evolve. A large proportion of the LGBTQI+ community does not disclose their gender identity or sexual orientation to health care workers. For instance, one study revealed that 73% were reluctant to share their transgender identity with their physician because of fear of discrimination.[16]

The care of patients who are LGBTQI+ and have epilepsy is particularly challenging because there is a paucity of epidemiologic studies and literature to guide evaluation and treatment. Respecting a patient's gender identity and asking about their name and the pronouns they use can help to establish trust and encourage frank conversation. Awareness and clarification of current terminology for sexual orientation and gender identity is important. It is crucial to understand the difference between gender identity, gender expression, and sexual orientation because these concepts describe a person's sense of self in terms of gender, an individual's external expression of gender, and sexual attraction. Gender identity may not be visible to others. A transgender person describes an individual whose gender identity differs from the sex they were assigned at birth.

Practitioners should be aware of LGBTQI+ community-specific challenges. Although no current studies exist on the rates of stigma, depression, and anxiety in people with epilepsy, one study in the United States showed that the rate of suicide attempts in transgender people was more than 25 times that of the general population.[17] A 2022 prospective observational cohort study found that gender-affirming care reduced depression (60% lower odds) and suicidality (73% lower odds) over a 12-month follow-up.[18]

Transgender people have unique health care needs in terms of reproductive health. A 2017 article by Johnson and colleagues[19] reviews the various gender-affirming treatments and potential interactions with antiseizure medications. The authors highlighted the challenges encountered by the health care team in managing this type of treatment in people with epilepsy. Gender-affirming treatment in transfeminine people includes gonadotropin-releasing hormone analogs or progestin as well as estrogen. If the transition occurs during adulthood, an antiandrogen such as spironolactone is prescribed in addition to estrogen. The gender-affirming treatment of transmasculine people uses progestin or a gonadotropin-releasing hormone analog. For adults seeking treatment, testosterone is prescribed, and progestin can be added if menstruation does not stop with testosterone alone. When transfeminine people with epilepsy are prescribed estrogen, there is a theoretical risk of increased seizures because estrogen has proconvulsant properties. If lamotrigine is prescribed as an antiseizure medication, the levels must be closely monitored and the dose adjusted because estrogen can increase its metabolism (both lamotrigine and estrogen are metabolized via glucuronidation). Hormonal gender-affirming treatments for transgender people have the potential for interactions with antiseizure medications.

KEY POINTS

- **The treatment of sexual dysfunction in people with epilepsy may require changing antiseizure medication.**
- **Patients living with epilepsy come from diverse backgrounds and may face unique challenges and disparities in care.**
- **A large proportion of the lesbian, gay, bisexual, transgender, queer or questioning, intersex, and more (LGBTQI+) community does not disclose their gender identity or sexual orientation to health care workers.**
- **Respecting a patient's gender identity and asking about their name and the pronouns they use can help to establish trust and encourage frank conversation.**
- **A 2022 prospective observational cohort study found that gender-affirming care reduced depression (60% lower odds) and suicidality (73% lower odds) over a 12-month follow-up.**

The social stigma associated with epilepsy can be exacerbated by the stigma against people who are LGBTQI+. A judicious choice of antiseizure medications must be made after a careful evaluation of patients' psychiatric comorbidities to prevent exacerbation of depression or other psychiatric disorders. Another consideration is the elevated substance misuse rate, possibly as a result of depression and stress among people who are LGBTQI+.[20]

The LGBTQI+ community living with epilepsy faces several unique challenges many of which have been attributed to inadequate health care workers' knowledge. A better understanding of the unique health care needs of people who are LGBTQI+ and have epilepsy will lead to culturally competent care as well as improved outcomes.

REPRODUCTIVE HEALTH

Reproductive health and family planning in people with epilepsy can be complex and require several considerations and frequently a multidisciplinary approach as highlighted in the following sections.

CASE 9-1

A 25-year-old woman presented with a history of generalized epilepsy for 10 years and migraines, both well controlled with topiramate. She was seen in consultation to establish care. Her last tonic-clonic seizure was 2 years ago after she ran out of her medication. A previous trial of levetiracetam led to irritability. When the neurologist inquired if she was taking daily folic acid supplementation, the patient stated that she was not planning to become pregnant in the next year but may consider it in a couple of years. Additionally, she noted that she was in a relationship with a woman.

COMMENT

This case highlights several considerations for people of childbearing potential in whom topiramate is being used as a dual agent for epilepsy management and migraine prophylaxis. Any encounter with a patient of reproductive potential is an opportunity to counsel about optimal management and reproductive outcomes if the patient is planning to become pregnant. This patient may not be planning to become pregnant in the next year, but she is considering a pregnancy in the future. Her circumstances may change over time; therefore, it is pertinent to inform her about the potential risks of her treatment for pregnancy. At high doses (200 mg and more daily), topiramate has enzyme-inducing properties and may render hormonal birth control methods ineffective. Additionally, topiramate is associated with teratogenic risks. Zonisamide is a broad-spectrum antiseizure medication with a similar mechanism of action as topiramate and it would be a reasonable treatment alternative. Zonisamide has a lower teratogenic risk and less enzyme-inductive potential, and it may assist in preventing the patient's migraines. Clinicians should take an inclusive sexual history before recommending folic acid and counseling about the risk of teratogenicity associated with antiseizure medications.

Family Planning

The American Academy of Neurology (AAN) created standardized quality measures for providers, practices, and health care systems, with the goal of improving the delivery of care for people with epilepsy. The measures include counseling people with epilepsy of childbearing potential (12 years and older) about the need for folic acid supplementation, drug-to-drug interactions with contraception, and potential antiseizure medication effects on fetal and child development as well as pregnancy (CASE 9-1).[21]

Reproductive health care includes access to birth control as well as safe abortion care. There are several important interactions between antiseizure medications and hormonal contraception that need to be carefully considered in people with epilepsy during their reproductive years. The following sections will highlight these special considerations.

FOLIC ACID. Periconception folic acid supplementation reduces the risk of neural tube defects. In people with epilepsy of childbearing potential, folic acid supplementation before and during pregnancy is associated with a decreased risk of miscarriage and preterm birth.[22] In addition, folic acid supplementation during preconception and pregnancy appears to offer other benefits, including improved cognitive and behavioral outcomes.[23-26] Certain antiseizure medications such as valproic acid and its derivatives such as divalproex sodium, carbamazepine, phenobarbital, phenytoin, and lamotrigine interfere with folate metabolism. Valproic acid in particular has been shown to target folate receptors, decreasing brain and placenta uptake of folic acid metabolites.[27]

Although there is no consensus on the optimal folic acid dose, the consensus is 1 mg to 2 mg of folic acid daily before and during pregnancy. Some authors suggest that patients taking valproate or carbamazepine should be prescribed a higher dose of folic acid. In 2009, the AAN released guidelines recommending the prescription of at least 0.4 mg daily of folic acid (up to 4 mg) to people with epilepsy of childbearing potential from puberty to menopause.[28] A 2022 observational study caused concerns among clinicians treating people with epilepsy of childbearing potential because the authors reported an association between high-dose folic acid (1 mg/d or more) prescriptions to pregnant people with epilepsy and an increased risk of cancer in their children.[29] This article sparked a debate and several concerns related to the repercussions of these findings, such as influence on clinical decision making during preconception counseling of people with epilepsy of childbearing potential, patient adherence to supplementation during pregnancy, and the potential effect on guidelines. Von Wrede and colleagues highlighted the methodologic flaws of this study and noted that the results suggested only an association rather than a causal relationship.[30] Experts recommend supplementing people with epilepsy of childbearing potential with at least 0.4 mg daily of folic acid periconceptually and during pregnancy. In May 2024, the AAN published an updated practice guideline providing evidence-based recommendations addressing the effects of antiseizure medications and folic acid supplementation on the prevalence of major congenital malformations and adverse perinatal and neurodevelopmental outcomes in children born to people with epilepsy (TABLE 9-2).[31]

CONTRACEPTION. Certain antiseizure medications may increase the risk of contraceptive failure, and estrogen-based contraception may increase the

KEY POINTS

- A better understanding of the unique health care needs of people who are LGBTQI+ and have epilepsy will lead to culturally competent care as well as improved outcomes.
- The American Academy of Neurology (AAN) created standardized quality measures for providers, practices, and health care systems, with the goal of improving the delivery of care for people with epilepsy.
- In people with epilepsy of childbearing potential, folic acid supplementation is associated with a decreased risk of miscarriage and preterm birth.
- Folic acid supplementation preconception and during pregnancy appears to offer improved cognitive and behavioral outcomes.
- Experts recommend supplementing people with epilepsy of childbearing potential with at least 0.4 mg daily of folic acid around the time of conception and during pregnancy.
- When used in combination with oral contraceptive drugs, higher doses of topiramate (200 mg/d or more) can lower ethinyl estradiol serum concentrations and decrease the effectiveness of contraceptive drugs.

potential of breakthrough seizures (TABLE 9-3). Hormonal contraception may be ineffective when enzyme-inducing antiseizure medications are prescribed. Estrogen-containing hormonal contraception accelerates the glucuronidation pathway of lamotrigine and, to a lesser extent, valproate, resulting in lower concentrations of these antiseizure medications. This interaction can increase the risk of breakthrough seizures especially when lamotrigine is used with hormonal contraceptive methods. When used in combination with oral contraceptive drugs, higher doses of topiramate (200 mg/d or more) can lower ethinyl estradiol serum concentrations and decrease the effectiveness of contraceptive drugs.[32]

Intrauterine devices (IUDs) are highly effective forms of reversible contraception without antiseizure medication drug interactions. The progestin-containing IUD is long-acting and considered to be a safe and acceptable choice for people with epilepsy of childbearing potential.[33] One study analyzed retrospective data from the Epilepsy Birth Control Registry web-based survey of people with epilepsy of childbearing potential in the community and found that 78.9% of women reported having at least one unintended pregnancy.[34] The authors also found that among reversible contraceptive categories, the IUD had the lowest failure rate of 3.1%. In contrast, the failure rate was 15.2% for hormonal contraception and 12% for barrier contraception. This study also revealed health disparities because unintended pregnancy was more common among younger, racial minority, and Hispanic people with epilepsy of childbearing potential. Barrier methods such as condoms are the only method that decreases the risk of

TABLE 9-2

Recommendations for Prenatal Folic Acid Supplementation and Antiseizure Medications[a]

Clinicians should

- Recommend preconception antiseizure medications and doses that optimize both seizure control and fetal outcomes should pregnancy occur
- Prescribe at least 0.4 mg daily of folic acid before preconception and during pregnancy to any people with epilepsy of childbearing potential treated with an antiseizure medication
- Exercise caution in attempting to remove or replace an antiseizure medication that is effective in controlling convulsive seizures if a person with epilepsy of childbearing potential is already pregnant

Clinicians must

- Avoid the use of valproic acid in people with epilepsy of childbearing potential to reduce the risk of poor neurodevelopmental outcomes, including autism spectrum disorder and lower IQ in children born to people with epilepsy of childbearing potential
- Avoid the use of valproic acid in people with epilepsy of childbearing potential to minimize the risks of major congenital malformations, neural tube defects, and the risk of offspring being born small for gestational age
- Consider using lamotrigine, levetiracetam, or oxcarbazepine in people with epilepsy of childbearing potential when appropriate based on the epilepsy syndrome, likelihood of achieving seizure control, and comorbidities
- Minimize the occurrence of convulsive seizures in people with epilepsy of childbearing potential during pregnancy to minimize potential risks to parent and fetus

[a] Data from Pack AM, et al, Neurology.[31]

sexually transmitted diseases. If used consistently and properly, condoms are approximately 95% effective.[35] They can be used alone or in combination with other contraceptive methods.

ABORTION. In 2022, the United States Supreme Court ended federal protection of the right to an abortion by returning abortion regulation to each individual state. Neurologists and health care providers who treat people with epilepsy of childbearing potential must be aware of their state's specific regulations when participating in prenatal counseling.

Pregnancy, Delivery, and Postpartum Care

The challenge of treating people with epilepsy of childbearing potential during pregnancy is balancing the fetal and maternal risks associated with seizures against the exposure to potential teratogenic antiseizure medications.

MEDICAL MANAGEMENT. Because a substantial number of pregnancies are unplanned, prepartum counseling should start as the first antiseizure medication is prescribed to people with epilepsy of childbearing potential. Data from the Epilepsy Birth Control Registry found that 65% of pregnancies were unintended, which emphasizes the importance of choosing an antiseizure medication that is compatible with the patient's preferred method of birth control.[34] Pregnancy planning and conception care can result in better outcomes for the fetus and birthing parent.

Most data from two of the largest registries revealed that lamotrigine and levetiracetam had the lowest rates of major congenital malformations followed by oxcarbazepine.[36,37] EURAP (European and International Registry of

Interactions Between Antiseizure Medications and Hormones TABLE 9-3

Antiseizure medications that decrease estrogen and progestin levels

- Carbamazepine
- Cenobamate
- Clobazam
- Eslicarbazepine
- Felbamate
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rufinamide
- Topiramate

Antiseizure medications that decrease progestin levels

- Perampanel

Antiseizure medication levels that are decreased by combined oral contraception

- Lamotrigine
- Valproic acid

Antiepileptic Drugs in Pregnancy) is a prospective observational study that analyzed the data of 7355 pregnancies exposed to one of eight commonly used antiseizure medications. The prevalence of major congenital malformations was the highest for valproate (10.3%), followed by phenobarbital (6.5%), phenytoin (6.4%), carbamazepine (5.5%), and topiramate (3.9%) (FIGURE 9-1). The risk of major congenital malformations was equal to or less than 3% for oxcarbazepine, lamotrigine, and levetiracetam. The prevalence of major congenital malformations increased with the dose at the time of conception for valproate, carbamazepine, lamotrigine, and phenobarbital.

In addition to the risk of major congenital malformations, the fetal risks induced by exposure to certain antiseizure medications include intrauterine growth restriction. The effect on intrauterine growth varies between different antiseizure medications and appears to be most pronounced with topiramate (18.5%), but it also increases with exposure to phenobarbital and possibly zonisamide.[38]

In terms of the cognitive effects of antiseizure medications, the MONEAD (Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs) study suggests that adaptive functioning of children of people with epilepsy taking commonly used antiseizure medications does not significantly differ from that of children of women who do not have epilepsy.[39] The NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study examined the fetal antiseizure medication exposure effects on learning and memory functions in 221 six-year-old children whose mothers took four commonly used antiseizure medications during pregnancy: carbamazepine, lamotrigine, phenytoin, and valproate.[40] This study revealed that children exposed to valproate experienced significant difficulty in their ability to process, encode, and learn both auditory and verbal as well as visual and nonverbal material. A significant decrease in

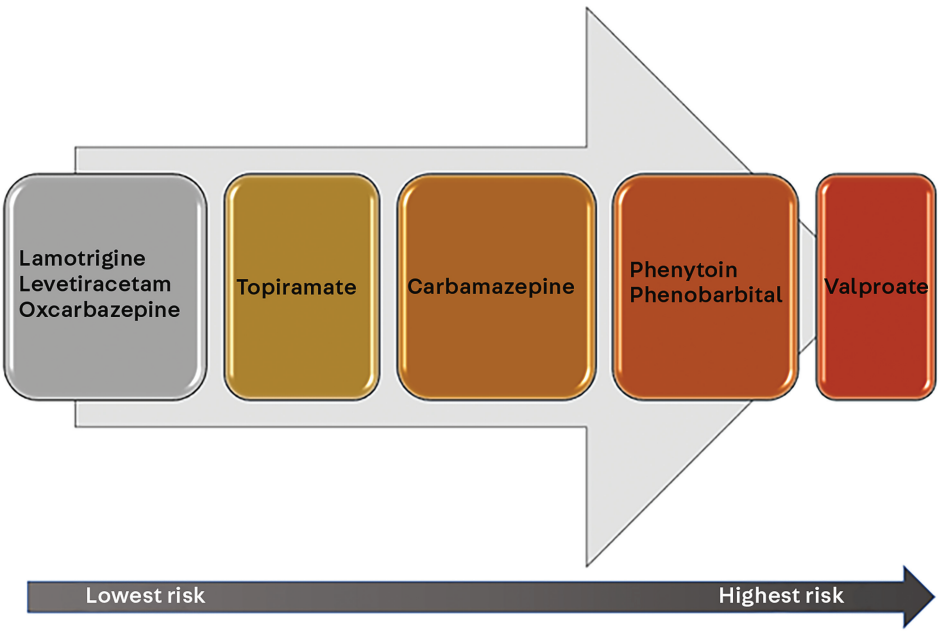

FIGURE 9-1
Antiseizure medications and risk of major congenital malformations.

functioning was seen with increasing third-trimester maximum antiseizure medications serum concentrations.

There is a paucity of data regarding the effect on the offspring of fathers who used antiseizure medications during conception. Few studies have shown evidence that antiseizure medications used by fathers before conception may increase the risk of adverse neonatal outcomes.[41] In a 2021 study, the authors found that 18% of children born to fathers on antiseizure medications experienced developmental delays compared with 2% of controls; however, this result was not statistically significant.[42] The authors did not find statistically significant differences in the rates of developmental disorders and birth weight among the offspring of men with epilepsy taking antiseizure medications at the time of conception when compared with controls.

PREGNANCY. Up to 0.5% of all pregnancies occur among people with epilepsy of childbearing potential.[43] Historically, people with epilepsy of childbearing potential were thought to have lower birth rates when compared with people of childbearing potential without epilepsy. However, these studies failed to take into consideration biological and social factors. A 2018 multicenter cohort study found that people with epilepsy of childbearing potential had a similar likelihood of achieving pregnancy within 1 year after enrollment as their peers without epilepsy.[44]

Communication and close collaboration between the neurology team and the obstetric team are essential when caring for pregnant people with epilepsy. It is important to note that seizure freedom for at least 9 months before pregnancy is associated with a high rate (84% to 92%) of remaining seizure free during pregnancy.[28] The MONEAD study group showed that there were no differences between pregnant people with epilepsy of childbearing potential and nonpregnant people with epilepsy of childbearing potential in terms of increase in seizures or severity of the seizures.[45] This study found that during pregnancy, the dose of antiseizure medications was changed at least once in 74% of pregnant patients and in 31% of controls.

Pregnancy can have a major effect on the pharmacokinetics of antiseizure medications. These alterations affect absorption, increase volume of distribution, induce hepatic metabolism, and elevate renal excretion. A decrease in the serum concentration of certain antiseizure medications can affect seizure control, which can affect the health of the birthing parent and potentially the fetus. Tonic-clonic seizures are dangerous to both the birthing parent and fetus as a result of hypoxemia and blunt trauma.[46] The MONEAD study revealed that there is a significant gestational decrease in antiseizure medication serum concentrations of lamotrigine, levetiracetam, lacosamide, oxcarbazepine, topiramate, and zonisamide.[47] The serum concentration of lamotrigine was lower in the second and third trimester than in the first trimester. The clearance of lamotrigine is most likely due to estrogen-driven enhanced glucuronidation during pregnancy. The serum concentrations for carbamazepine and valproic acid remain fairly stable throughout pregnancy. Data for other newer antiseizure medications is insufficient. The data from the MONEAD study supports therapeutic drug monitoring early in pregnancy. In line with these findings, the authors of a retrospective single-center study recommend early and close monitoring of antiseizure medication levels in patients with an established diagnosis of drug-resistant epilepsy before pregnancy.[48] The International

KEY POINTS

- In May 2024, the AAN published an updated practice guideline providing evidence-based recommendations addressing the effects of antiseizure medications and folic acid supplementation on the prevalence of major congenital malformations and adverse perinatal and neurodevelopmental outcomes in children born to people with epilepsy.
- Progestin-containing intrauterine devices are long-acting and considered to be a safe and acceptable choice for people with epilepsy of childbearing potential.
- Neurologists and health care providers who treat people with epilepsy of childbearing potential and participate in prenatal counseling must be aware of their state's specific abortion regulations.
- Because a substantial number of pregnancies are unplanned, prepartum counseling should start when the first antiseizure medication is prescribed to people with epilepsy of childbearing potential.
- Children exposed to valproate experienced significant difficulty in their ability to process, encode, and learn both auditory and verbal as well as visual and nonverbal material.
- There is a paucity of data regarding the effect on the offspring of fathers who used antiseizure medications during conception.

League Against Epilepsy Task Force on Women and Pregnancy reinforces these recommendations.[49]

Pregnant patients who take antiseizure medications are at a higher risk of preterm birth (lower than 37 weeks gestational age) and small for gestational age newborns.[38] Among pregnant people who used monotherapy antiseizure medication, the prevalence of small for gestational age ranged from 7.3% for lamotrigine monotherapy to 18.5% for topiramate monotherapy. A 2020 prospective study revealed that epilepsy is a significant risk factor for preterm delivery, cesarean delivery, fetal hypoxia, and an Apgar score less than or equal to 7 at 5 minutes for the offspring of people with epilepsy of childbearing potential compared with controls.[50] Seizures experienced during pregnancy seem to influence the preference for a cesarean delivery. A systematic review and meta-analysis showed that greater use of antiseizure medications was associated with poor outcomes.[51] The authors of this study concluded that people with epilepsy of childbearing potential should receive pregnancy counseling from an

CASE 9-2

A 35-year-old man presented for a second opinion regarding antiseizure medication side effects. His wife accompanied him. He was diagnosed with posttraumatic focal epilepsy in his late 20s. His seizures have been well controlled after the addition of pregabalin to oxcarbazepine. His last seizure was 7 months ago after the dose of pregabalin was further optimized. He and his wife are trying to conceive a child. He has noted over the past couple of months occasional difficulties with maintaining an erection and was wondering if this could be related to his antiseizure medications. He also expressed concerns about the effect of the antiseizure medications he takes on conception. He noted that this is causing a great deal of anxiety. He denied depression. He looked forward to having a child and stated that he was planning to be a "hands-on dad."

COMMENT

This case illustrates several points. Antiseizure medications have been shown to alter reproductive hormone levels but also sexual function. There are reports of pregabalin leading to erectile dysfunction. It is possible that the increase in the dose of this antiseizure medication contributed to his symptoms. A decrease in the dose could be attempted while monitoring for breakthrough seizures. If his symptoms persist, a change in medication should be considered as well as a referral to a urologist. Sexual function also can be improved by addressing and managing his anxiety. With regard to developmental disorders in the offspring of fathers with epilepsy, there are no robust data to support this risk, and no registries exist with relevant data for this population. In terms of parenting, the patient and his wife should be counseled about safety measures to prevent injuries to the patient and their baby. It is best to dress and change the baby on the floor with a changing pad and avoid the use of a changing table. Regarding bath time, parents with epilepsy should be advised to sponge-bathe the baby on a changing pad on the floor rather than bathing them in a tub with water. Parents should be advised to use a padded carrycot rather than a baby carrier.

epilepsy specialist who can also optimize their antiseizure medications before and during pregnancy.

PERIPARTUM AND POSTPARTUM PERIOD. Epilepsy is not considered an indication for cesarean delivery unless the birthing parent is unable to follow instructions or has altered consciousness because of a seizure during labor.[49] If antiseizure medication dosing has been increased during pregnancy, the rate of taper of the antiseizure medication after delivery back to the prepregnancy dose depends on the individual drug and degree of seizure control, particularly for lamotrigine.

In the peripartum and postpartum period, in addition to adjusting antiseizure medication doses when indicated, the health care team should counsel people with epilepsy about safety precautions while changing, bathing, and transporting their babies (CASE 9-2).

NEUROSTIMULATION. The management of epilepsy is not limited to antiseizure medications. People with drug-resistant epilepsy may benefit from neurostimulation therapy. Three neurostimulation therapies are used as adjunctive therapy for drug-resistant epilepsy: vagus nerve stimulation, responsive neurostimulation, and deep brain stimulation. Despite the use of vagus nerve stimulation therapy worldwide, only a few studies reported on use during pregnancy. A group of small case series found that vagus nerve stimulation appears to be safe during pregnancy for the patient and fetus, with a tendency of increased obstetric complications, mostly cesarean deliveries.[52–54] A case report found that deep brain stimulation appears to be safe without any effect on pregnancy outcomes.[55] A short case series found no major congenital malformations in the offspring of people with epilepsy who were treated with responsive neurostimulation during pregnancy.[56]

KETOGENIC DIETS AND DIETS FOR EPILEPSY. People with drug-resistant epilepsy may also benefit from special diets. Although ketogenic diets have been successfully used in the management of drug-resistant epilepsy, the effect of ketones on fetal development is unclear. Ketones can cross the placenta, and patients with gestational diabetes mellitus are often advised to avoid diets that result in elevated ketone levels.[57] Elevated ketone levels during pregnancy have been associated with adverse fetal outcomes such as a decreased childhood IQ, oligohydramnios, and fetal heart rate irregularities. Two cases of pregnant people with epilepsy treated with ketogenic diets have been described, but the effects of the diets were inconclusive.[58] During the December 2023 American Epilepsy Society annual meeting, speakers noted that the North American Pregnancy Registry is collecting data on low glycemic and ketogenic diets.

BREASTFEEDING. The American Academy of Pediatrics recommends that all babies be exclusively breastfed for at least the first 6 months of life.[59] The MONEAD study revealed that mothers with epilepsy were less likely to initiate breastfeeding compared with controls. However, when accounting for maternal IQ and education there was no significant difference between the cohorts.[60] The total amount of antiseizure medication transferred to infants via breast milk is usually much less than the amount transferred via the placenta during pregnancy. The International League Against Epilepsy Women Task Force determined that phenobarbital and probably lamotrigine and zonisamide are extensively

KEY POINTS

- Up to 0.5% of all pregnancies occur among people with epilepsy of childbearing potential.
- A decrease in the serum concentration of certain antiseizure medications can affect seizure control, which can affect the health of the birthing parent and potentially the fetus.
- According to one study, the serum concentration of lamotrigine is lower in the second and third trimesters of pregnancy than in the first trimester.
- The serum concentrations for carbamazepine and valproic acid remain fairly stable throughout pregnancy.

transferred into breast milk.[61] Given the benefits of breastfeeding to both the birthing parent and baby, people with epilepsy should be encouraged to consider breastfeeding. However, as drug elimination mechanisms are not fully developed in early infancy, parents should be counseled to closely monitor their babies for excessive sedation.

Catamenial Epilepsy and Menopause

As already noted, epilepsy and hormones have complicated interactions and additional management challenges can be encountered during two particular situations in people with epilepsy.

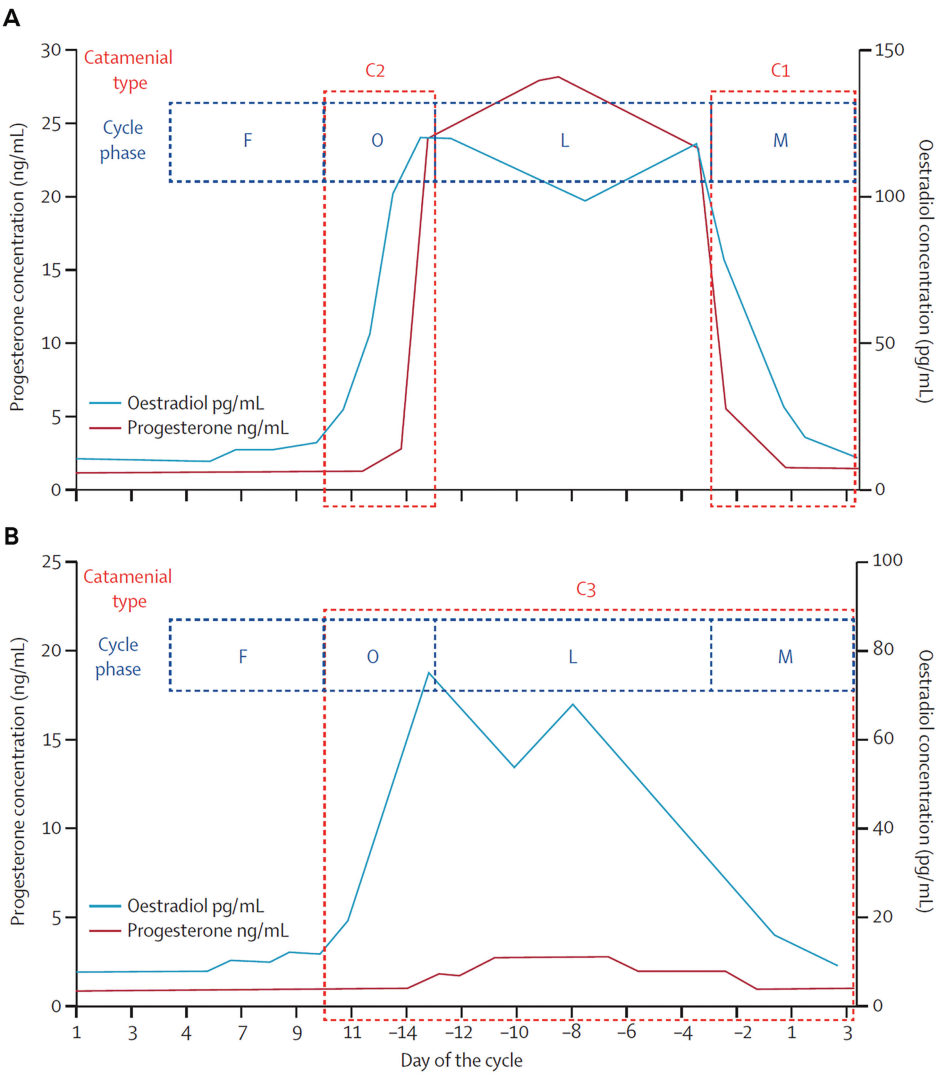

FIGURE 9-2

Hormone changes and catamenial seizure patterns during the menstrual cycle. Day 1 is the first day of menstrual flow; day -14 is ovulation. *A*, The C1 pattern represents perimenstrual seizure exacerbation, and the C2 pattern represents periovulatory seizure exacerbation. *B*, The C3 pattern represents catamenial epilepsy in anovulatory cycles.

F = follicular phase; L = luteal phase; M = perimenstrual phase; O = periovulatory phase.

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CATAMENIAL EPILEPSY. There is a reciprocal relationship between seizures and sex steroids. Catamenial epilepsy is described as a pattern of seizure exacerbation related to the menstrual cycle, and it may affect approximately 40% of people with epilepsy of childbearing potential.[62,63] Seizure exacerbation can be observed perimenstrually (C1 pattern), at ovulation (C2 pattern), and during the luteal phase (C3 pattern).[64] A reduction in progesterone levels is implicated in patterns C1 and C3, whereas a preovulatory surge in estrogen is involved in the C2 pattern (FIGURE 9-2).

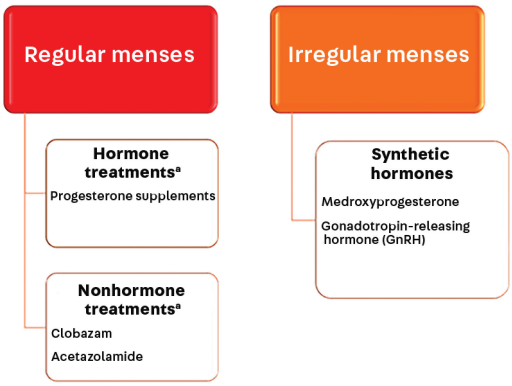

FIGURE 9-3
Treatment strategies for catamenial epilepsy.
[a] Treatments taken before and during menses.

The diagnosis of catamenial epilepsy is made if the seizure frequency increases by at least twofold during a certain phase of the cycle in two out of three consecutive cycles.[65] Treatment strategies depend on whether the patient has regular or irregular menstrual cycles (FIGURE 9-3).[66] Based on the findings of a large-scale, randomized, placebo-controlled, multicenter hormonal treatment trial, progesterone shows efficacy superior to placebo in patients whose seizures show robust perimenstrual exacerbation.[63]

MENOPAUSE. Menopause is considered to have occurred when a person has gone a full year without menses. People typically experience menopause between the ages of 45 and 55 years.[67] Perimenopause can last up to 5.5 years, includes the first year after cessation of menses, and is marked by hormonal fluctuations. There is an increased risk of an early onset of perimenopausal symptoms in people with epilepsy. The hormonal changes during perimenopause may also be associated with seizure exacerbation in people with epilepsy of childbearing potential who experienced a catamenial seizure pattern.[68] In contrast, these patients may experience an improvement in seizure occurrence during menopause.[69] Administration of hormone replacement therapy to relieve the symptoms associated with menopause can be considered in consultation with a gynecologist. Hormone replacement therapy is available either as estrogen alone or estrogen combined with progesterone. Patients should be counseled to report side effects and seizure exacerbations once hormone replacement therapy is initiated.[70] Nonestrogen-based therapies and vaginal lubricants should be considered if symptoms worsen with hormone replacement therapy.

CONCLUSION

Epilepsy often requires treatment with lifelong antiseizure medications. Epilepsy and epilepsy management can significantly affect quality of life. The balance between risks and benefits of various treatments should be evaluated on an individual basis. Seizures, seizure management, and the hormone shifts that take place throughout the lifespan of people with epilepsy of childbearing potential,

KEY POINTS

- Pregnant patients who take antiseizure medications are at a higher risk of preterm birth (lower than 37 weeks gestational age) and small for gestational age newborns.
- If antiseizure medication dosing has been increased during pregnancy, the rate of taper of the antiseizure medication after delivery back to the prepregnancy dosing depends on the individual drug and seizure control, particularly for lamotrigine.
- The health care team should counsel people with epilepsy about safety precautions while changing, bathing, and transporting their babies.
- Given the benefits of breastfeeding to both the birthing parent and baby, people with epilepsy should be encouraged to consider breastfeeding.
- Catamenial epilepsy is described as a pattern of seizure exacerbation related to the menstrual cycle, and it may affect approximately 40% of people with epilepsy of childbearing potential.
- Hormonal changes during perimenopause may be associated with seizure exacerbation in patients who experienced a catamenial seizure pattern.

especially those who plan to have children, can dramatically affect sexual and reproductive health, contraception, pregnancy, and childbirth. The safety and seizure control of nonpharmacologic epilepsy therapies during pregnancy, such as the use of neurostimulation or ketogenic diets, would benefit from further study. Further monitoring and standardized registries of pregnant people with epilepsy and patients who use diets to help manage epilepsy are needed as well as registries for special populations, including people with epilepsy from the LGBTQI+ community. Sexual dysfunction side effects related to the use of antiseizure medications have not received sufficient attention. People with epilepsy have lower reproductive rates, and the causes are multifactorial, including psychological and physiologic causes, with epilepsy and antiseizure medications playing a role. Improving health care workers' knowledge about the challenges that people with epilepsy face and awareness of management strategies are essential parts of patient-centered care.

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