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Gynecologic Management of Adolescents and Young Women With Seizure Disorders

ABSTRACT: Seizure disorders frequently are diagnosed and managed during adolescence; therefore, obstetrician–gynecologists who care for adolescents should be familiar with epilepsy and other seizure disorders, as well as antiepileptic drugs. Patients diagnosed with seizure disorders during childhood may have increased seizure activity with puberty and menarche due to the neuroactive properties of endogenous steroid hormones. Compared with patients without epilepsy, patients with epilepsy are more likely to experience anovulatory cycles, irregular menstrual bleeding, and amenorrhea. Although hormonal suppression should not be initiated before puberty or menarche, prepubertal counseling may be appropriate, and obstetrician–gynecologists may work with young patients and their families to develop a plan to initiate with menarche. Additionally, obstetrician–gynecologists should be aware of any medication changes, including antiepileptics, for adolescent patients with seizure disorders. Research on hormonal therapy for the treatment of epilepsy is scant; however, the anticonvulsant properties of various progestins have been explored as potential treatment. There is no conclusive evidence that combination hormonal contraception increases epileptic seizures, and epilepsy itself poses no increased risk of an adverse outcome for those using combined oral contraceptive pills, the contraceptive patch, or a contraceptive ring. Because many antiepileptic drugs are teratogenic, discussing sexual health with and providing effective contraceptive choices to this population is critical. Obstetrician–gynecologists should work with patients with seizure disorders to develop a plan when pregnancy occurs.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists makes the following recommendations and conclusions regarding gynecologic management of adolescents and young women with seizure disorders:

- Seizure disorders frequently are diagnosed and managed during adolescence; therefore, obstetrician–gynecologists who care for adolescents should be familiar with epilepsy and other seizure disorders, as well as antiepileptic drugs.
- With the onset of menses, seizures may increase and both the condition and its therapies influence reproductive health, including contraceptive choice, contraceptive efficacy, and the menstrual cycle.
- Adolescents with seizure disorders require ongoing education about potential adverse pregnancy outcomes and the most effective contraceptive options. Ideally, education should begin in early adolescence and continue throughout a patient's reproductive lifespan because antiepileptic drugs, contraceptive needs, and desire for pregnancy may change over time.
- The risk of poor pregnancy outcomes is primarily due to the teratogenicity of some antiepileptic drugs. Although pregnant patients with epilepsy who are nonmedicated have a similar fetal malformation rate as the general population, fetal antiepileptic drug exposure is associated with a twofold to threefold increased risk of major congenital malformations,

with even higher rates reported with valproate or polytherapy use.

- Collaboration with a neurologist is important when initiating or changing hormonal therapy, whether for birth control, menstrual suppression, or other medical indications, because these hormonal medications may have a bidirectional interaction on enzyme-inducing antiepileptic drugs.
- Many patients, particularly those with refractory seizures, will use polytherapy with antiepileptic drugs, making drug interactions more likely.
- First-line treatment for seizure disorders is anticonvulsant medication; hormonal therapy is an adjunct approach.
- In standard doses, depot medroxyprogesterone acetate (DMPA) administration has been shown to decrease seizure frequency.
- A levonorgestrel-containing intrauterine device (IUD) is a safe and effective option in adolescents and young women with seizure disorders who desire menstrual improvement or contraception.
- When enzyme-inducing antiepileptic drugs cannot be avoided, patients should be counseled to simultaneously use barrier methods (eg, condoms) with combination hormonal contraceptives to decrease the risk of contraceptive failure.
- The use of combined oral contraceptive pills (OCPs) with lamotrigine has been shown to reduce lamotrigine concentrations by 50%, increasing the risk of seizures. Furthermore, lamotrigine levels rise during the pill-free interval, which could contribute to adverse effects. When the use of lamotrigine and combination hormonal contraceptives cannot be avoided, dose adjustments with lamotrigine may be needed or extended cycle use of contraception can be considered, or both.
- All methods of emergency contraception can be used without restriction in adolescents and young women with seizure disorders or those using antiepileptic drugs.
- For those patients planning to become pregnant, consultation with a neurologist to optimize medication choice to decrease teratogenic potential is appropriate.

Introduction

Seizure disorders include a wide range of clinical conditions associated with seizures, including epilepsy, brain infections and tumors, and traumatic brain injury. Epilepsy, a neurologic syndrome characterized by recurrent convulsive seizures that usually start during childhood or adolescence, affects about 6.4 per 1,000 individuals in the general population (1, 2). Seizure disorders frequently are diagnosed and managed during adolescence; therefore, obstetrician-gynecologists who care for adolescents should be familiar with epilepsy and

other seizure disorders, as well as antiepileptic drugs. With the onset of menses, seizures may increase and both the condition and its therapies influence reproductive health, including contraceptive choice, contraceptive efficacy, and the menstrual cycle. Patients diagnosed with seizure disorders during childhood may have increased seizure activity with puberty and menarche due to the neuroactive properties of endogenous steroid hormones (3). Endogenous estrogens have proconvulsant and epileptogenic properties, although the mechanism by which estradiol increases neuronal excitability is not well understood (4). Natural serum progesterone has been found to reduce seizures, and a decrease in progesterone or progesterone-estradiol ratio during specific times of an ovulatory menstrual cycle is associated with increased seizure activity (4).

Compared with patients without epilepsy, patients with epilepsy are more likely to experience anovulatory cycles, irregular menstrual bleeding, and amenorrhea (5); both the epileptic discharges and the antiepileptic drugs have been implicated as potential causes of these menstrual abnormalities (5–7). Antiepileptic drugs themselves may affect reproductive health as well as contraceptive choice and efficacy; some antiepileptic drugs are teratogens (Table 1). Prospective studies have found evidence of the development of polycystic ovary syndrome among some adolescents using valproic acid, a commonly used antiepileptic drug (8, 9). Studied mechanisms include valproic acid directly increasing ovarian androgen production or causing inhibition of testosterone metabolism (10).

Collaboration with a neurologist is important when initiating or changing hormonal therapy, whether for birth control, menstrual suppression, or other medical indications, because these hormonal medications may have a bidirectional interaction on enzyme-inducing antiepileptic drugs. The neurologist may change a patient's antiepileptic drugs based on contraceptive choice, desire for pregnancy, or reproductive health-related adverse effects. Many patients, particularly those with refractory seizures, will use polytherapy with antiepileptic drugs, making drug interactions more likely. The same considerations apply when antiepileptic drugs are used for mood stabilization, migraine prophylaxis, neuropathic pain, or bipolar disorder.

Catamenial Seizures

Catamenial seizures refer to cyclic seizure exacerbation in relation to the menstrual cycle (11, 12). The most accepted definition of *catamenial epilepsy* is a twofold increase in the baseline average daily seizure activity during a particular phase of the menstrual cycle (11). Catamenial epilepsy is diagnosed by an evaluation of a menstrual and seizure diary. More than one third of postmenarchal girls and women with medication-refractory epilepsy experience catamenial seizure exacerbation (3).

Table 1. Obstetric and Gynecologic Considerations of Antiepileptic Drugs*

Drug	Malformation Risk	Most Frequent Major Malformation	Gynecologic Considerations
Valproic acid	4.7–10%	Neural tube defects, hypospadias, cardiac anomalies	Use associated with development of polycystic ovary syndrome
Topiramate	4.2–7.7%	Orofacial clefts	Dosages less than 200 mg do not affect levels of oral contraceptive pills containing 35 micrograms ethinyl estradiol
Phenobarbital	5.5–7.4%	Cardiac anomalies	<ul style="list-style-type: none"> • Potent liver enzyme inducer • Decreases efficacy of combination contraception
Phenytoin	2.9–6.7%	Cardiac anomalies	<ul style="list-style-type: none"> • Potent liver enzyme inducer • Decreases efficacy of combination contraception
Carbamazepine	2.6–5.6%	Cardiac anomalies	<ul style="list-style-type: none"> • Potent liver enzyme inducer • Decreases efficacy of combination contraception
Lamotrigine	2.0–3.4%	Cardiac anomalies, orofacial clefts	<ul style="list-style-type: none"> • Combination oral contraceptive pills can reduce lamotrigine concentrations by 50%, increasing the risk of seizures. • Dose adjustments may be needed
Oxcarbazepine	1.8–3.3%	Orofacial clefts [†]	<ul style="list-style-type: none"> • Potent liver enzyme inducer • Decreases efficacy of combination contraception
Levetiracetam	0–2.4%	Cardiac anomalies [†] , neural tube defects [†]	Does not affect the prescribing of hormonal contraceptives
Acetazolamide	Limited data do not indicate a risk of malformation	—	<ul style="list-style-type: none"> • Limited data on decreasing catamenial seizures • Does not affect the prescribing of hormonal contraceptives
Cannabis-based products (cannabidiol or “CBD”) [‡]	No data	No data	Effect on contraceptive efficacy, teratogenic potential is unknown

*Data from the following registries: International Register of Antiepileptic Drugs and Pregnancy, North American Antiepileptic Drug Pregnancy Register, UK Epilepsy and Pregnancy Register, Medical Birth Register of Norway, Swedish Medical Birth Register.

[†]Rarely reported.

[‡]Currently there is one cannabidiol oral solution approved by the U.S. Food and Drug Administration for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients 2 years of age and older.

Modified from Gooneratne IK, Wimalaratna M, Ranaweera AKP, Wimalaratna S. Contraception advice for women with epilepsy; with permission from BMJ Publishing Group Ltd. *BMJ* 2017;357:j2010.

The menstrual cycle variation in steroid hormone levels and ratios correlates with the timing of seizures in catamenial epilepsy. The most common seizure pattern is perimenstrual, occurring 3 days before menses and the first 3 days of menses, when progesterone levels drop in ovulatory cycles (13). Perioovulatory catamenial exacerbation has been attributed to the midcycle surge of estrogen that is relatively unopposed by progesterone (14). Patients have fewest seizures during the midluteal phase in ovulatory cycles when progesterone levels are the highest (13).

Adjuvant Treatment for the Management of Seizure Disorders

First-line treatment for seizure disorders is anticonvulsant medication; hormonal therapy is an adjunct

approach. Research on hormonal therapy for the treatment of epilepsy is scant; however, the anticonvulsant properties of various progestins have been explored as potential treatment. Older studies that have used oral or vaginal preparations administered during the luteal phase demonstrated a reduction in seizure occurrence with catamenial epilepsy (15–17).

There are more data to support the use of DMPA to decrease the frequency of seizures. In standard doses, DMPA administration has been shown to decrease seizure frequency (18, 19). In a study of 14 women with refractory partial seizures and ovulatory cycles, standard DMPA administration at 150 mg every 12 weeks resulted in a 39% reduction in seizures (18). An observational study of 750 women (aged 18–47 years) within an

epilepsy birth control registry reported fewer seizures for patients using DMPA compared with those using OCPs or progestin-only pills (20). It is not well understood whether this reduction is because of low estrogen levels, lack of cyclic hormonal changes, lack of ovulation, the anticonvulsant properties of progesterone, or other benefits of amenorrhea, such as a decrease in dysmenorrhea. Amenorrhea rates with standard DMPA administration approaches 50–60% at 1 year, and shorter dosage intervals (administration every 8–10 weeks) can be used, if required, to decrease bleeding or catamenial seizures (21). Norethindrone acetate, although not approved for contraception, is another progestin that can be titrated to achieve amenorrhea for those in this population who are seeking menstrual suppression.

Small studies have reported decreased seizure frequency with the use of gonadotropin releasing hormone (GnRH) analogs among patients with refractory perimenstrual seizures (22, 23). These medications suppress estrogen levels and induce amenorrhea; however, an increase in seizures can occur during the first 3 weeks of therapy because of the estrogen flare before suppression (4). Use of GnRH analogs has not been studied in adolescents for this purpose and no long-term studies exist; GnRH analogs should be used with caution in adolescents due to concerns of decreasing bone density during a time of peak bone accrual and lack of data on duration of use.

New therapies for the treatment of seizure disorders include cannabis-based products such as cannabidiol (“CBD”). In a 2018 systematic review, evidence from randomized controlled trials suggested that CBD likely reduces seizures among children with drug-resistant epilepsy (24). The authors cautioned that the findings of this study were limited to CBD and should not be extrapolated to other cannabis products. Its effect on contraceptive efficacy and teratogenic potential are unknown. Currently there is one CBD oral solution approved by the U.S. Food and Drug Administration for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients 2 years of age and older (25).

General Contraceptive Considerations

Adolescents with seizure disorders require ongoing education about potential adverse pregnancy outcomes and the most effective contraceptive options. Ideally, education should begin in early adolescence and continue throughout a patient’s reproductive lifespan because antiepileptic drugs, contraceptive needs, and desire for pregnancy may change over time. Although hormonal suppression should not be initiated before puberty or menarche, prepubertal counseling may be appropriate, and obstetrician–gynecologists may work with young patients and their families to develop a plan to initiate with menarche. The American

Academy of Neurology has formally recognized discussion of these reproductive issues as a clinical quality measure and suggests these discussions begin at menarche (26). Studies show that patients with seizure disorders who are on antiepileptic drugs do not have adequate knowledge of antiepileptic drugs’ interactions with hormonal contraception and feel they receive insufficient counseling from their health care providers (27–30). Early discussion including family involvement may lay the foundation for improved knowledge, contraception use, and pregnancy planning as adolescents with seizure disorders transition to adult care. Education about the reproductive cycle, contraception, and pregnancy should begin early and be addressed at each visit.

The risk of poor pregnancy outcomes is primarily due to the teratogenicity of some antiepileptic drugs (Table 1). Although pregnant patients with epilepsy who are nonmedicated have a similar fetal malformation rate as the general population, fetal antiepileptic drug exposure is associated with a twofold to threefold increased risk of major congenital malformations, with even higher rates reported with valproate or polytherapy use (31). Thirty percent of patients with seizure disorders do not use highly effective contraception; this is a concern given their higher risk of having offspring with fetal malformations (32).

The Effects of Antiepileptic Drugs on Contraception

A substantial percentage of patients with epilepsy (46%) use systemic hormonal contraception, which may interact with some antiepileptic drugs, thus compromising their contraceptive efficacy (32). Compared with patients without epilepsy, patients with epilepsy have a higher contraception failure rate with OCPs (28, 33). One study of 300 women with epilepsy who reported a pregnancy found that most patients with epilepsy did not plan their pregnancies and OCP failure was the cause of one-in-four unintended pregnancies (34).

Combination Hormonal Contraceptive Methods

There is no conclusive evidence that combination hormonal contraception increases epileptic seizures (35, 36), and epilepsy itself poses no increased risk of an adverse outcome for those using combined OCPs, the contraceptive patch, or a contraceptive ring. Combination hormonal contraceptive methods are considered category 1 (no restriction for the use of the contraceptive method) according to the Centers for Disease Control and Prevention’s U.S. Medical Eligibility Criteria (USMEC) for women with epilepsy (37). However, for those taking specific anticonvulsants, combined hormonal contraception is considered a USMEC category 3 (the theoretical or proven risks usually outweigh the advantages of using the method) due to the likely reduction

of contraceptive effectiveness. For patients taking medications listed in Box 1, special consideration should be given for contraception. The concern with combination hormonal contraceptive use is specific to concomitant use of hepatic enzyme-inducing antiepileptic drugs. Many antiepileptic drugs (Box 1) induce cytochrome P450 enzymes or uridine-diphosphate-glucuronosyltransferase enzymes, or both, which accelerate the metabolism of reproductive steroids (38). Lowered serum concentrations of estrogen and progesterone increase the risk of contraceptive failure (39). Therefore, combination hormonal contraception in women using enzyme-inducing antiepileptic drugs is a USMEC category 3 (37). For adolescents who are not sexually active and only desire menstrual improvement, combination contraception can be used for menstrual suppression alone; counseling on the contraceptive efficacy of the method should occur as the patient's needs change.

Potent inducers of hepatic enzymes include antiepileptic drugs such as carbamazepine, primidone, phenobarbital, and phenytoin. Other antiepileptic drugs, such as topiramate, are less potent inducers and the extent of enzyme induction may be dose-dependent (38). Topiramate therapy at dosages less than 200 mg daily does not affect pharmacokinetic levels of OCPs that contain 35 micrograms of ethinyl estradiol (40). Typical doses of topiramate used to treat other disorders, such as migraines (25–50 mg), are not considered to decrease contraceptive efficacy.

Historically, because of concerns about decreased contraceptive efficacy with the use of combination OCPs and enzyme-inducing antiepileptic drugs, the following recommendations have been suggested: 1) prescribing high-dose OCPs (greater than 35 micrograms); 2) prescribing extended cycle OCPs; and 3) decreasing the hormone-free interval in sequential pills to less than 7 days to minimize the risk of escape ovulation (41–43). None of these recommendations are evidence-based. When enzyme-inducing antiepileptic drugs cannot be avoided, patients should be counseled to simultaneously use barrier methods (eg, condoms) with combination hormonal contraceptives to decrease the risk of contraceptive failure.

Combination hormonal contraceptive use in patients taking lamotrigine poses unique challenges and requires close collaboration with a neurologist. Lamotrigine is metabolized by hepatic uridine-diphosphate-glucuronosyltransferase enzymes that are inducible by ethinyl estradiol. The use of combined OCPs with lamotrigine has been shown to reduce lamotrigine concentrations by 50%, increasing the risk of seizures (44, 45). Furthermore, lamotrigine levels rise during the pill-free interval, which could contribute to adverse effects (36). When the use of lamotrigine and combination hormonal contraceptives cannot be avoided, dose adjustments with lamotrigine may be needed or extended cycle use of contraception can be considered, or both (46).

Box 1. Classification of Antiepileptic Drugs

Liver Enzyme Inducers

- Carbamazepine
- Felbamate
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Primidone
- Rufinamide

Noninducers of Liver Enzymes

- Clobazam
- Clonazepam
- Ethosuximide
- Ezogabine*
- Gabapentin
- Lacosamide
- Lamotrigine†
- Levetiracetam
- Pregabalin
- Tiagabine
- Topiramate‡
- Valproate
- Vigabatrin
- Zonisamide

*The production of ezogabine has been discontinued and it is no longer available.

†Lamotrigine does not affect levels of ethinyl estradiol. Although lamotrigine lowers C_{max}, area under the curve, and trough levels of the progestin levonorgestrel, the changes are very small and unlikely to affect efficacy.

‡Topiramate given at a dose of 200 mg a day does not affect levels of norethindrone. Topiramate decreases area under the curve and C_{max}, but not trough levels of ethinyl estradiol when given at a dose of 200 mg a day.

Adapted from Davis AR, Pack AM, Dennis A. Contraception for women with epilepsy. In: Allen RH, Cwiak CA, editors. Contraception for the medically challenging patient. New York, NY: Springer; 2014. p. 135–46.

Progestin-Only Methods and Antiepileptic Drugs

Enzyme-inducing antiepileptic drugs do not change the efficacy of DMPA or a levonorgestrel-containing IUD. These methods are rated as USMEC category 1 for patients with seizure disorders regardless of the use of antiepileptic drugs (37). Depot medroxyprogesterone acetate previously has been advocated as first-line contraceptive choice in patients with seizure disorders due to reported reduction in seizure frequency and low risk of

contraceptive failure (47). However, a levonorgestrel-containing IUD is a safe and effective option in adolescents and young women with seizure disorders who desire menstrual improvement or contraception (21, 48, 49). The contraceptive efficacy of the 52 mg levonorgestrel IUD has been observed to remain high with concomitant use of enzyme-inducing antiepileptic drugs (50).

Overall, the etonogestrel implant has a very high contraceptive efficacy; thus, the risk of failure likely remains low compared with other contraceptive methods (41). However, because a pharmacokinetic study of 13 women demonstrated significant reductions in serum etonogestrel concentrations in patients using carbamazepine (51), the USMEC rates concomitant anticonvulsants and the etonogestrel implant as a category 2 (a condition where the advantages of using the method generally outweigh the theoretical or proven risks) (37). Although progestin-only pills (0.35 mg norethindrone) may be used for menstrual improvement (21), their use as a contraceptive method is rated category 3 in patients using enzyme-inducing antiepileptic drugs (37). This precaution for potential interaction also applies to a new progestin-only pill containing 4 mg of drospirenone.

Emergency Contraception

All methods of emergency contraception can be used without restriction in adolescents and young women with seizure disorders or those using antiepileptic drugs. Additionally, the copper IUD is considered a category 1 in this population (37) and can be used as an emergency or long-term form of contraception. Levonorgestrel and ulipristal acetate emergency contraceptives are rated category 2 among women using CYP3A4 inducers; this is due to theoretical risks of reduced efficacy but, to date, no studies of concomitant anticonvulsant use exist (37).

Prepregnancy Counseling and Obstetric Considerations

Obstetrician–gynecologists should work with patients with seizure disorders to develop a plan when pregnancy occurs. The plan should include not immediately stopping antiepileptic drugs if a patient becomes pregnant. For those patients planning to become pregnant, consultation with a neurologist to optimize medication choice to decrease teratogenic potential is appropriate.

Other Considerations

Obstetrician–gynecologists should counsel adolescent and adult patients to use condoms for the prevention of sexually transmitted diseases regardless of concomitant contraceptive method. Additionally, obstetrician–gynecologists should be aware of any medication changes, including antiepileptics, for adolescent patients with seizure disorders. Communication with the patient’s neurologist is helpful to provide ongoing and accurate counseling regarding reproductive health-related concerns as well as contraceptive

choice and efficacy. Obstetrician–gynecologists should be aware that long-term use of antiepileptic drugs may negatively affect bone mineral density (52).

Conclusion

Adolescents and young women with seizure disorders and their families require ongoing counseling regarding the potential effects of both the condition and antiepileptic drugs on their reproductive health. Because many antiepileptic drugs are teratogenic, discussing sexual health with and providing effective contraceptive choices to this population are critical. Collaboration with a neurologist when either initiating or changing contraceptive methods is important because of the potential bidirectional interaction between some antiepileptic drugs and combination hormonal contraceptives. Some enzyme-inducing antiepileptic drugs decrease the contraceptive efficacy of combination hormonal contraceptives. Enzyme-inducing antiepileptic drugs have no effect on the contraceptive efficacy of DMPA or of levonorgestrel-containing or copper IUDs.

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