Review Article

Women and Epilepsy

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Women with epilepsy face additional challenges when compared to their peers. Hormonal influences may increase seizure activity, alter endocrine function, and affect fertility. In this population, antiepileptic drugs (AEDs) reduce the efficacy of contraception methods and increase the risk of fetal malformations. Other pertinent issues to women with epilepsy include breastfeeding as well as bone mineral health. This article summarizes our current, collective knowledge of these issues and makes specific recommendations with respect to management.

KEYWORDS antiepileptic drugs, breastfeeding, epilepsy, female, review, treatment

INTRODUCTION

Epilepsy is a chronic neurological condition of unprovoked, recurrent seizures. The disorder affects approximately 1% of the population, including over one million women of childbearing age.[1] Women with epilepsy face additional challenges secondary to hormonal influences on seizure activity and endocrine function. In addition, antiepileptic drugs (AEDs) play a significant role regarding contraception, pregnancy/breastfeeding and bone health. The following discussion details potential complications and treatment dilemmas of women with epilepsy.

CATAMENIAL EPILEPSY

Catamenial epilepsy may be defined as a 2-fold increase in seizure occurrence during or just prior to menses.[2-4] Depending on the method of data collection and definition used, the incidence of catamenial epilepsy ranges from 10%-78%.[5,6] Herzog and colleagues described three patterns of catamenial epilepsy—perimenstrual, periovulatory and luteal.[7,8] They further reported seizure patterns of 184 females with refractory complex partial seizures as related to their ovulatory cycle.

ABBREVIATIONS AED, antiepileptic drugs; PCOS, polycystic ovarian syndrome

Using the definition of a 2-fold increase in seizure frequency during menses, it was concluded that nearly one third of women with intractable complex partial seizures may have catamenial epilepsy.[8]

Elevated estrogen or decreased progesterone levels can exacerbate seizure frequency. More specifically, progesterone or its metabolites (allopregnanolone) have been found to inhibit neuronal excitability through the modulation of GABA A receptors.[9,10] Estrogen is believed to promote seizure activity by enhancing the NMDA receptor in the hippocampus.[11] The most vulnerable time for catamenial seizures in an ovulatory female is immediately prior to ovulation and prior to menses, when estrogen/progesterone ratios are high. In an anovulatory female, catamenial seizures typically occur during the latter half of the menstrual cycle due to unopposed elevated estrogen levels.

Treatment for catamenial seizures should begin with increasing the dosage of the prescribed AED

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in order to sustain a higher and more effective serum concentration. If side effects develop, the next approach would be to provide alternative medication. Acetazolamide, a mild diuretic, has been used "off-label" as an adjunctive agent since the 1950's. While the exact anti-epileptic effect is unknown, a 50% or greater reduction in catamenial seizure frequency has been retrospectively reported in 40% of patients taking acetazolamide.[12] Acetazolamide may be given immediately before and during menses at a dose of 4 mg/kg/day (not to exceed 1 g/day) in divided doses.[9]

Alternative therapies include perimenstrual clobazam (20-30 mg/day),[13] combined oral contraception pills[14] or progesterone.[15] Cyclic progesterone supplementation in lozenge or suppository form (100-200 mg TID) has been shown to significantly improve catamenial epilepsy. This hormone was found to be most beneficial when given during the second half of the menstrual cycle. Progesterone should be tapered off over 3-4 days at the end of the cycle to prevent rebound catamenial seizures.[16,17]

CONTRACEPTION

The efficacy of hormonal contraception may be diminished for women taking CYP-450 enzyme inducing AEDs, such as phenobarbital, phenytoin, carbamazepine and topiramate. These AEDs interact with combined estrogen/progesterone oral contraceptive pills. Increased hepatic metabolism can produce up to a 5-fold increase in contraception failure rates.[18,19] The mechanism responsible for diminished contraceptive effectiveness involves an increase in estrogen and/or progestin metabolism which can reduce circulating hormone levels by as much as 50%.[20-26] Progesterone-only birth control pills or levonorgestrel implants may be an ineffective method of birth control for women taking CYP-450 enzyme inducing AEDs for this reason.[12,15] Medroxyprogesterone depot injections can also be affected by CYP-450 enzyme inducing AEDs. Therefore, these injections need to be given more frequently in women taking this class of AEDs.[27] Contraception alternatives for patients taking CYP-450 enzyme inducing AEDs include either high dose (50-100 mcg) estrogen agents, barrier contraception methods, or intrauterine devices to minimize the risk of unintended pregnancy.[27,28]

There is now a new intrauterine copper T device that has been approved for nulliparous women.

Lamotrigine has been shown to decrease the efficacy of combined oral contraceptive pills by reducing the concentration of the progestin component. Furthermore, it has been suggested that progesterone-only pills can increase lamotrigine levels,[29] although a more recent study has not replicated these findings.[30] Conversely, a decrease of up to 70% in lamotrigine trough serum concentrations were noted in patients on combined hormonal contraception. However, during the placebo week or when a patient discontinues oral hormonal contraception, lamotrigine trough concentrations increase nearly 2-fold.[31] As a result, lamotrigine concentrations should be closely monitored in women taking oral contraceptive pills. Alternatively, patients may encounter fewer variances in AED levels by utilizing continuous hormonal contraception without a placebo.

Non-enzyme inducing AEDs, such as valproate sodium, benzodiazepines, ethosuximide, zonisamide, levetiracetam, vigabatrin, gabapentin, pregabalin and tiagabine, do not interfere with the effectiveness of combined hormonal contractive pills.[11,32]

Emergency contraception through the use of high dose progestins may be initiated following unprotected intercourse. While no study has examined the ideal dose for women taking AEDs, current recommendations are levonorgestrel 1.5 mg immediately following intercourse and 0.75 mg 12 hours later.[33]

Reproductive Dysfunction

Women with epilepsy frequently experience reproductive abnormalities, specifically anovulatory cycles, menstrual irregularities and endocrine dysfunction. The etiologies are multifactorial but may result from altered hormonal functioning of the hypothalamus, pituitary, or ovaries as a result of the presence of seizures or AED exposure.[34] Fertility can be reduced by 20% to 40% when compared to women without seizures.[35,36] A common cause of infertility is polycystic ovarian syndrome (PCOS). Signs and symptoms of the condition include obesity, hypercholesterolemia, hirsuitism, acne, irregular periods, infertility and hypertension from circulating unbound androgens. Although polycystic ovaries are sometimes seen in these patients, their presence is not mandatory to make the diagnosis

of PCOS. The term PCOS is used when there is evidence of anovulatory cycles and elevated serum androgen levels. The syndrome is estimated to cause infertility in 4%-7% of women but is 2-3 times higher in women with epilepsy, particularly primary generalized epilepsy.[37-40]

Multiple asymptomatic ovarian cysts have been detected in 21%-23% of women.[32,41,42] Studies have suggested that women with epilepsy are at higher risk for developing multiple ovarian cysts with detection rates ranging from 26%-41%.[43-45] Primary generalized epilepsy, the use of valproate and obesity increase the risk of polycystic ovaries.[39,46] Although not necessarily given the diagnosis of PCOS, up to 60% of women with epilepsy treated with valproate have multiple cysts in their ovaries. The prevalence in this cohort is highest in women receiving valproate prior to their mid-20s.[47,48] Valproate, as part of a polytherapy regimen, appears to increase the risk of ovarian cysts more than monotherapy.[49] Simultaneous administration of oral contraceptive pills with valproate may be protective.[50] Women with polycystic appearing ovaries who are switched from valproate to another AED may demonstrate involution of ovarian cysts.[39,41] Replacing valproate with lamotrigine resulted in normalization of endocrine function in 75% of women with polycystic ovaries, hyperandrogenism or both.[41] The use of valproate within the preceding three years has been shown to produce nearly four times the increased risk of ovulatory failure when compared to women not taking the medication.[51] Anovulatory cycles increase the risk of infertility among women in the reproductive age.

Pregnancy

Seizure frequency can increase in 17%-33% of women during pregnancy.[52,53] Furthermore, seizure control may become difficult to manage in an additional 15%-35%.[54-58] This finding occurs with all types of epilepsy and is not related to seizure control during previous pregnancies.[48] The risk of status epilepticus is 1%-2% during pregnancy.[59,60] Seizure frequency is highest during labor and delivery, seen in approximately 5% of women.[52,55] Another 1% will have seizures up to 24 hours after delivery.[51]

Many factors must be evaluated when treating pregnant women with epilepsy. Decisions include whether to continue AED treatment and, if so, which medications pose the least risk to the mother and fetus. Optimizing AEDs becomes more challenging during pregnancy due to sleep deprivation, medication compliance and alterations in pharmacokinetics. Changes in serum AED concentration are the result of decreased binding to plasma proteins and enhanced drug elimination.[61,62] Although the total AED concentration falls due to increased plasma volume and total body water, there is an increase in free (unbound) drug titers due to a reduction in albumin.[63,64] This is especially seen with phenytoin, phenobarbitol, valproate, carbamazepine and lamotrigine. As a result, unbound serum levels should be measured and compared to pregestational values. We recommend monitoring AED levels once every trimester, at delivery, and one to two weeks after delivery.

Counseling the patient regarding the treatment of epilepsy during pregnancy is essential due to the teratogenic potential of AEDs. Since a significant percentage of pregnancies are unplanned, it is important to discuss these issues with all women with epilepsy of childbearing age prior to conception. Antiepileptic medications have been shown to contribute to a higher rate of birth defects and learning disabilities.[65,66] However, the discontinuation of AEDs may increase the risk of seizures, which can be harmful to both the mother and fetus. The maternal death rate is 10 times higher in women with epilepsy as compared to women without. The risk is believed to be secondary to an increased rate of seizures due to either subtherapeutic AED levels or a change in medication regimen.[61] A general guideline is that a single, low-dose agent is preferred to polytherapy.[67] Holmes et al demonstrated an increased rate of "anticonvulsant embryopathy" in infants exposed to anticonvulsant drugs during gestation. The risk to the infant was directly correlated to the number of AEDs taken by the mother during pregnancy.[68]

The risk of fetal malformation in the general population is 2%-4%. Prenatal exposure to AEDs is known to increase this risk to 4%–9%.[63,69-73] Cardiac defects are seen in patients exposed to barbiturates, phenytoin or carbamazepine. The risk of a neural tube defect is associated with in utero exposure to carbamazepine (1%) and valproate (1%-2%).[74-77] Genitourinary and/or skeletal anomalies have also been seen with valproate.[78] In at least one pregnancy registry, the risk of isolated cleft lip/palate is noted with fetal exposure to lamotrigine.[79]

Multiple large scale studies demonstrate a dose-dependent and increased rate of fetal malformations following maternal valproate usage as compared to other AEDs.[63,65,66,80,81] The North American Antiepileptic Drug Pregnancy Registry showed the risk of congenital malformations in fetuses exposed to valproate during the first trimester is higher than for all other forms of monotherapy.[82] Similarly, the UK Epilepsy and Pregnancy Registry showed an increased birth defect incidence with valproate when compared to carbamazepine.[65] The International Lamotrigine Pregnancy Registry reported that major fetal malformations are four times more likely to occur when patients receive polytherapy including valproate versus those on lamotrigine monotherapy or polytherapy not including valproate.[83] Therefore, in order to attempt to minimize the risk of fetal defects, the lowest possible monotherapy dose should be sought prior to conception. Due to the use of supplemental folic acid, the incidence of neural tube defects in the United States has declined.[84] As a result, women with epilepsy are recommended to take 2-4 mg/day of folic acid. The dose should increase to 4 mg/day for those taking valproate due to elevated risk of fetal defects with this drug.[85]

With respect to the newer antiepileptic medications, including lamotrigine, levetiracetam, topiramate, zonisamide and felbamate, the exact risks of fetal malformation during pregnancy remain unknown. There are a number of pregnancy registries that are currently ongoing and will provide credible percentage risks for fetal malformations in the next two years.

Breastfeeding

Most health organizations recommend breastfeeding due to the numerous benefits to the child, including reducing infections and decreasing the risk of immunological disorders.[86] The American Academy of Neurology also supports breastfeeding in women taking AEDs with close monitoring.[87] Although the amount of drug in breast milk is usually less than that delivered through the placenta, the infant's organs may not yet be equipped to metabolize AEDs. Phenobarbitol, ethosuximide and primidone are found in high concentration in breast milk and should be used with caution.[81] Lamotrigine and zonisamide are also secreted in breast milk. One study demonstrated that infant lamotrigine concentrations at 2

weeks of age were 30% of the maternal drug concentrations.[88] Zonisamide concentration in breast milk is similar to maternal serum concentration.[11] The lactated concentration levels of phenytoin, carbamazepine and valproate are 3%-5% of the therapeutic dose and can be considered safer alternatives.[81,82] Of the newer AEDs, levetiracetam secretion in breast milk is significantly lower than maternal plasma values.[89]

While breastfeeding, AED concentrations may fluctuate due to increased metabolism and rates of clearance. As a result, AED concentrations need to be monitored while breastfeeding. In addition, as breastfeeding is weaned AED concentrations may increase and therefore, doses may need to be altered. Breastfed infants showing signs of lethargy, decreased feeding or weight loss should have serum AED concentrations measured.[12]

Bone Health

When compared to the general population, women with epilepsy are at increased risk of falls, fractures, osteoporosis and osteopenia.[90-92] Seizures are a known cause of fractures in patients with epilepsy due to an increased susceptibility to falls.[93] Mattson and Gidal reported a 2-6 fold increase in fractures in patients treated with AEDs.[94] Furthermore, AEDs have been shown to have a detrimental effect on bone quality.[95] Several studies found decreased serum calcium and/or vitamin D concentrations in patients treated with enzyme inducing AEDs.[96-98] Other studies did not duplicate these findings.[92,99] Bone mineral density is lower in women with epilepsy, especially those patients older than 40 years of age taking enzyme inducing AEDs longer than two years.[100] In addition, AEDs that do not induce CYP-450 enzymes are also linked to osteopenia.[101] Women with epilepsy tend to reach menopause at an earlier age, thus contributing to bone loss.[102] Animal studies have shown detrimental changes in bone quality after treatment with levetiracetam, phenytoin or valproate.[103]

Mikati and colleagues demonstrated that high dose vitamin D supplementation (4000 international units for adults and 2000 international units for children) in patients on long term antiepileptic medications increased bone mineral density.[104] These findings suggest that female patients on chronic AED therapy should strongly consider high dose vitamin D supplementation.

Other treatments include hormone replace-

Table. Clinical Pearls Regarding Antiepileptic Use in Women

- Catamenial epilepsy occurs in many women with epilepsy. Treatment for catamenial seizures should begin with a sustained increase in the patient's antiepileptic medication. Alternative adjunctive therapies include acetazolamide, oral contraceptives or progesterone.

- The efficacy of hormonal contraception diminishes in women who are taking CYP-450 enzyme inducing AEDs. Medroxyprogesterone depot injections can also be affected by CYP-450 enzyme inducing AEDs. Women taking CYP-450 enzyme inducing AEDs should use a higher dose of estrogen contraceptive drugs (50-100 µg), have more frequent depot injections or use barrier contraception methods. The new copper T intrauterine device has been approved in nulliparous women and may be an attractive alternative. None of these methods, except for barrier contraception methods, prevent sexually transmitted diseases.

- Women with epilepsy have a higher risk of reproductive dysfunction, including polycystic ovarian syndrome, multiple ovarian cysts, anovulatory cycles and infertility. These findings are more profound in women taking valproate.

- Women with epilepsy who are on AEDs and pregnant have an increased risk of fetal malformations. Prenatal exposure to AEDs is known to increase this risk to 4-9%. However, the vast majority of women with epilepsy deliver healthy babies. In addition, the cessation of AEDs during pregnancy increases the risk of seizures, including status epilepticus. In order to minimize the risk of fetal malformations, the lowest possible monotherapy AED dose should be sought prior to conception. In addition, all women of child-bearing age should have folate supplementation of 2-4 mg, 4 mg in women with epilepsy who are on valproate.

- Breastfeeding in women taking AEDs is safe, providing that there is close monitoring of the baby for potential side effects.

- Women with epilepsy are at higher risk for osteoporosis and fractures in comparison to their peers. Vitamin D and calcium supplementation are critical for maintenance of healthy bones. Bone mineral density should be routinely obtained in women with epilepsy.

ment therapy, bisphophonates, estrogen receptor modulators and calcitonin. Large doses of vitamin D therapy in patients using AEDs did result in increased bone density.[105,106] There continue to be many different treatment options; however, the most effective regimen has still not been determined. Due to the risks of potential bone loss in women receiving AEDs, bone density should be routinely monitored, especially in those with additional risk factors for poor bone health.

CONCLUSIONS

Treating women with epilepsy can be challenging. The clinician needs to be thoughtful about the choice of antiepileptic medications as it may effect reproductive planning and metabolic health. Careful and frequent assessments need to be made from menarche onward. A list of Clinical Pearls can be found in the Table.

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