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Best Practice Guidelines for the Management of Women with Epilepsy

Pamela Crawford

Department of Neurology, York District Hospital, York, United Kingdom

Summary: Being a woman with epilepsy is not the same as being a man with epilepsy. Epilepsy affects sexual development, menstrual cycle, aspects of contraception, fertility, and reproduction.

Menstrual cycle, epilepsy, and fertility: The diagnosis of epilepsy and the use of antiepileptic drugs (AEDs) present women of childbearing age with many problems; both the disease and its treatment can alter the menstrual cycle and fertility.

Contraception in epilepsy: There are no contraindications to the use of nonhormonal methods of contraception in women with epilepsy (see Table 3). Nonenzyme-inducing AEDs (valproate sodium, benzodiazepines, ethosuximide, and levetiracetam) do not show any interactions with the combined oral contraceptive pill. There are interactions between the COCP and hepatic microsomal-inducing AEDs (phenytoin, barbiturates, carbamazepine, topiramate [doses above 200 mg/day], and oxcarbazepine) and also lamotrigine.

Sexuality: The majority of women with epilepsy appear to have normal sex lives, although in some women with epilepsy, both the desire and arousal phases may be inhibited.

Preconception counseling: Preconception counseling should be available to all women with epilepsy who are considering pregnancy. Women with epilepsy should be aware of a number of issues relating to future pregnancy, including methods and consequences of prenatal screening, genetics of their seizure disorder, teratogenicity of AEDs, folic acid and vitamin K supplements, labor, breast feeding, and childcare.

Pregnancy: The lowest effective dose of the most appropriate AED should be used, aiming for monotherapy where possible. Recent pregnancy databases have suggested that valproate is significantly more teratogenic than carbamazepine, and the combination of valproate sodium and lamotrigine is particularly teratogenic. Most pregnancies are uneventful in women with epilepsy, and most babies are delivered healthy with no increased risk of obstetric complications in women.

Breast feeding: All women with epilepsy should be encouraged to breastfeed their babies. The AED concentration profiled in breast milk follows the plasma concentration curve. The total amount of drug transferred to infants via breast milk is usually much smaller than the amount transferred via the placenta during pregnancy. However, as drug elimination mechanisms are not fully developed in early infancy, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant.

The care of children of mothers with epilepsy: Although there is much anxiety about the possible risks to a child from the mother's epilepsy, there is little published evidence. The risk of the child being harmed depends on the type of seizure and its severity and frequency, and this risk is probably small if time is taken to train mothers and caregivers in safety precautions.

Menopause: During menopause, about 40% of women report worsening of their seizure disorder, 27% improve, and a third had no change. Hormone replacement therapy is significantly associated with an increase in seizure frequency during menopause, and this is more likely in women with a history of catamenial epilepsy.

Bone health: Women with epilepsy are at increased risk of fractures, osteoporosis, and osteomalacia. **Key Words:** Menstrual cycle—Fertility—Contraception—Reproduction—Pregnancy—Menopause—Polycystic ovary syndrome—Antiepileptic drug.

Being a woman with epilepsy is not the same as being a man with epilepsy. Epilepsy affects sexual development, menstrual cycle, aspects of contraception, fertility, and reproduction in ways that are unique to women. This review incorporates revised statements of guidelines for women with epilepsy based on those produced by a British panel, predominantly of neurologists. These statements are both evidence and experience-based, and the recommendations require judgment with regard to their applicability in individual circumstances (1,2). As with any guidelines, each statement has been assigned a level of evidence (I, II, or III), and each recommendation has been assigned a strength (A, B, or C) according to the level of supporting evidence (see Table 1). The criteria were based on a grading system adapted from the Canadian Task Force Classification (3).

Address correspondence and reprint requests to Dr. Pamela Crawford at Department of Neurology, York District Hospital, York YO31 8HE, United Kingdom. E-mail: pcrawford@doctors.org.uk

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TABLE 1. *Grading scheme for recommendation strengths and levels of evidence*

Level of evidence
I. Well-designed, randomized, controlled trials, systematic reviews or meta-analyses
II. Well designed (but nonrandomized), prospective, or retrospective controlled studies or other observational studies
III. Uncontrolled trials or descriptive studies or consensus agreed in reports from expert committees or other respected authorities
Strength of recommendations
A. Based directly on level I evidence
B. Based directly on level II evidence or extrapolated from level I evidence
C. Based directly on level III evidence or extrapolated recommendation from level I or II evidence

Adapted with permission (1).

MANAGEMENT AREAS SPECIFIC TO WOMEN

Adolescence and epilepsy

Adolescence is an important time to review the diagnosis of both epilepsy and the epilepsy syndrome because of the implications and decisions that may need to be made regarding antiepileptic drug (AED) treatment. Advice on relationships, contraception, and the consequences of AED treatment, employment, driving, and psychosocial issues such as alcohol use needs to be provided at this time (4).

Menstrual cycle, epilepsy, and fertility

The diagnosis of epilepsy and the use of AEDs present women of childbearing age with many problems; both the disease and its treatment can alter the menstrual cycle and fertility (see Table 2). Polycystic ovary syndrome (PCOS) is a syndrome of hyperandrogenism (with raised testosterone levels), multiple ovarian cysts, anovulatory cycles, hirsutism, and, in 30% to 50% of patients, obesity. The prevalence of PCOS in women without epilepsy is between 4% and 19%, depending on how the syndrome is defined and assessed (5). The true prevalence of the PCOS in women with epilepsy is unknown but is thought to be higher than in women without epilepsy, even in those not taking AED medication (4). PCOS is more common in women taking valproate sodium, especially those starting valproate before the age of 20 (6,7). Substituting lamotrigine or levetiracetam for valproate leads to a reversal of hyperinsulinaemia, hyperandrogenism, and low serum high-density lipoprotein cholesterol in the majority of women (8,9). Luteinizing hormone pulse frequency has been found to be increased (10) or variable in women with epilepsy (11), and this predisposes toward the development of PCOS (12).

Many studies have suggested that fertility is reduced in women with epilepsy. Some of this may be related to anovulatory cycles and/or hyperandrogenism, but most appears to be due to psychosocial factors (13).

Catamenial epilepsy

Catamenial seizures refer to an increase in seizures around the time of the menses, either just before or during the first few days of menstruation. Catamenial seizures are uncommon and occur in about 10% of women with epilepsy, but the majority claim that their seizures occur near the time of menstruation (4,14). Anovulatory cycles tend to be associated with an increase in seizure frequency in the second half of the menstrual cycle, while ovulatory cycles can have one or two peaks in seizure frequency around the time of menstruation and/or ovulation (15). Catamenial seizure exacerbations may be related to the changing sex hormone concentrations during the

TABLE 2. *Epilepsy, fertility, and the menstrual cycle*

Catamenial epilepsy—statements and recommendations
• Catamenial epilepsy occurs in about 12% of women with epilepsy (II)
• In ovulatory cycles, there may be two seizure peaks, perimenstrually and at mid cycle (II)
• For women already on AEDs, the currently recommended treatment is intermittent clobazam on days when seizure increase is anticipated (B); alternative therapies include acetazolamide given perimenstrually or progestogens (C)
• For women not already taking AEDs, the following are alternatives: intermittent perimenstrual clobazam (5 to 30 mg/day); COCP; depot progestogen therapy; or perimenstrual progestogen (III)
Fertility—statements and recommendations
• All women with epilepsy should be counseled about their fertility and the possible effects of their AED treatment (C)
• There is decreased fertility among women with epilepsy (II)
• The true prevalence of PCOS among women with epilepsy, even if they are not taking AEDs, may be higher than in women without epilepsy, and the prevalence is higher still in those taking valproate sodium (II)
Sexuality—statements and recommendations
• Sexual desire and sexual arousal may be affected by epilepsy or by the treatment of epilepsy in women (II)
• The majority of women with epilepsy have normal sex lives (II)
• Enquiry about sexual feelings and function should be part of the standard assessment of women with epilepsy (C)
• If a disorder of desire or arousal is discovered, expert psychological and neuroendocrine evaluations are recommended (C)

AED, antiepileptic drug; COCP, combined oral contraceptive pill; PCOS, polycystic ovary syndrome.

TABLE 3. *Contraception—statements and recommendations*

- There are no contraindications to the use of nonhormonal methods of contraception in women with epilepsy or the use of the Mirena coil (III)
- For women on nonenzyme-inducing AEDs (valproate sodium, benzodiazepines, vigabatrin, gabapentin, tiagabine, levetiracetam, pregabalin), all current contraceptive methods are suitable (III)
- Hormonal forms of contraception are affected by enzyme-inducing AEDs (phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate [>200 mg/day], and lamotrigine); women taking these forms of contraception should be counseled on their risks and benefits (C)
- For women on enzyme-inducing AEDs wishing to take the COCP:
  —Start with 50 μg/day ethinyl oestradiol dosage (C)
  —If breakthrough bleeding occurs, increase the dose of ethinyl oestradiol to 75 or 100 μg/day or consider giving three packs of the pill without a break ("tricycling") (C)
- Even on a higher-dose COCP with normal cycles, full oral contraceptive efficacy cannot be guaranteed in women with epilepsy taking enzyme-inducing AEDs (III)
- The progesterone only pill is likely to be ineffective in women taking enzyme-induced AEDs (III)

Medroxyprogesterone injections appear to be effective (III)

- There are no contraindications to the Mirena coil (III)
- Levonorgestrel implants are contraindicated (III)
- If appropriate, the emergency contraceptive pill can be used in women with epilepsy after unprotected sexual intercourse (C); a higher dose may be needed in women taking enzyme-inducing AEDs (C)
- Lamotrigine concentrations are lowered by the COCP (II)

AED, antiepileptic drug; COCP, combined oral contraceptive pill.

menstrual cycle (16). There are also alterations in AED concentrations, as seen with phenytoin and lamotrigine, throughout the menstrual cycle (17–20).

Many therapeutic interventions have been evaluated in catamenial epilepsy, with varying degrees of success. In the 1950s, acetazolamide was advocated and it is still used today in some patients. Over the past decade, there has been some research on hormonal manipulation, with the aim of increasing relative progesterone concentrations or converting anovulatory to ovulatory cycles (21,22). For women on AEDs, intermittent use of perimenstrual clobazam (5 or 10 mg) (23) or acetazolamide is suggested when a seizure increase is anticipated (4).

For women with catamenial epilepsy in whom low premenstrual progesterone levels may be a factor, an intermittent perimenstrual progesterone supplement is suggested, or a synthetic progestogen during days 10 to 26 of the menstrual cycle (1). A combined oral contraceptive pill (COCP) may be prescribed (1). Rarely danazol, goserelin, or clomiphene has been prescribed (1,24).

Contraception in epilepsy

There are no contraindications to the use of nonhormonal methods of contraception in women with epilepsy (see Table 3). Nonenzyme-inducing AEDs (valproate sodium, benzodiazepines, ethosuximide, zonisamide, and levetiracetam) do not show any interactions with the COCP (25). There are interactions between the COCP and hepatic microsomal-inducing AEDs (phenytoin, barbiturates, carbamazepine, topiramate [doses above 200 mg/day], and oxcarbazepine), leading to reduced contraceptive steroid concentrations and possible failure of contraception (4,25). A recent study has suggested a fall of norethisterone concentrations in patients receiving lamotrigine; therefore, women on a normal-dose COCP and lamotrigine may be at risk of unplanned pregnancies (26).

In women taking enzyme-inducing AEDs, the starting dose of ethinyl oestradiol should be 50 μg/day, and it may be necessary to increase the ethinyl oestradiol dose to 75 to 100 μg/day if breakthrough bleeding occurs. Women need advising that even on a higher-dose COCP, full contraceptive efficacy cannot be guaranteed. It must be assumed that the efficacy of progesterone-only oral contraceptives is affected by enzyme-inducing AEDs (4,25).

Although it was thought that there were no interactions between the COCP and lamotrigine, a 25–70% decrease in lamotrigine trough levels was reported recently in women taking the COCP, and a greater than 20% reduction was observed within 3 days of COCP ingestion in most patients. There was an increase in lamotrigine levels to between 80% and 100% of baseline in the pill-free week (27). A small reduction in lamotrigine concentrations (15% to 50%) was seen with a vaginal ring releasing ethinyl estradiol and etonogestrel (Nuvaring) (27). By contrast, lamotrigine concentrations were significantly increased (20% to 100%) by the concomitant administration of a progestogen-only oral contraceptive (desogestrel 75 μg [Cerazette]) (28).

Medroxyprogesterone injections appear to be an effective contraceptive in women with epilepsy, but patients are usually advised for these injections to be given every 10 weeks rather than 12 weeks if used in combination with enzyme-inducing AEDs (4). Levonorgestrel implants are contraindicated in women taking enzyme-inducing AEDs, since there is an unacceptably high failure rate (4). There are no contraindications to the Mirena coil in women with epilepsy, because progestogen acts by being released locally in the uterus (25).

If appropriate, the emergency contraceptive pill can be used in women with epilepsy after unprotected sexual intercourse. There are no data on whether a change in the dose of the morning-after contraceptive pill is required in women taking AED medication; some practitioners suggest a higher dose in those women taking enzyme-inducing AEDs (4,25).

Sexuality

The majority of women with epilepsy appear to have normal sex lives, although in some women with epilepsy, both the desire and arousal phases may be inhibited (4). It has been suggested that a short, standard sexual history (4) should form part of the assessment of all women with epilepsy.

Preconception counseling

Preconception counseling should be available to all women with epilepsy who are considering pregnancy (see Table 4). Women with epilepsy should be aware of a number of issues relating to future pregnancy, including methods and consequences of prenatal screening, genetics of their seizure disorder, teratogenicity of AEDs, folic acid and vitamin K supplements, labor, breast feeding, and childcare. The main aim of preconception counseling is to ensure that women embark upon pregnancy with a minimum of risk factors, fully aware of any risks and benefits of treatment, and able to make informed decisions about the pregnancy (4).

Seizure and AED management

Before conception, the continuing need for AED treatment should be reviewed. Women should enter pregnancy having complete seizure control or as few seizures as possible. If a patient has been seizure free for at least 2–3 years and does not have juvenile myoclonic epilepsy (JME), consideration may be given to withdrawing AEDs to reduce the potential teratogenic risk. Otherwise, the lowest effective dose of the most appropriate AED should be continued, aiming for monotherapy where possible and avoiding valproate sodium either as monotherapy or polytherapy (4).

As with all women contemplating pregnancy, advice should be given about maintaining good general health in relation to exercise, diet (including folic acid supplements), smoking, and alcohol consumption. Although a major concern of women with epilepsy is the teratogenic potential of AEDs, it is important to put these risks in perspective. Studies suggest that the risk of significant fetal malformation is approximately 3% if one AED is taken (slightly above the background risk) and up to 17 % if two or more AEDs are taken (4,29–31). Most major malformations develop at an early stage in pregnancy, often before the woman knows she is pregnant. AED exposure in the later stages of pregnancy may still lead to minor morphological abnormalities or specific learning difficulties (particularly in association with valproate sodium therapy) (32). The mechanisms whereby AEDs are teratogenic have not been definitely established. Since epilepsy is associated with increased risk of fetal malformations, women with epilepsy should be referred for a high-quality ultrasound scan at about 18 weeks to look for malformations. Recent pregnancy databases have suggested that valproate is significantly more teratogenic than carbamazepine, and the combination of valproate sodium and lamotrigine is particularly teratogenic (30,31).

Phenytoin

Phenytoin is particularly associated with an increased risk of cleft lip and palate as well as dysmorphic features such as nail and distal phalangeal hypoplasia and craniofacial abnormalities (4).

TABLE 4. *Preconception counseling and teratogenicity—statements and recommendations*

- Preconception information should be offered to all females with childbearing potential (C)
- If changes in AED medication are to be made, they should be completed before conception (B)
- If AED treatment is needed, a single agent is preferred (B)
- The risk of fetal malformation is increased in women receiving treatment for epilepsy compared with the general population (3% with carbamazepine or lamotrigine, 7% with valproate sodium, and 15% with two or more AEDs) (II)
- Most major malformations occur at an early stage in pregnancy, often before the woman knows she is pregnant (I)
- Women with epilepsy who are planning a pregnancy should take folic acid 5 mg/day in the preconception period and throughout the pregnancy (B); vitamin K should be used in the last month of pregnancy in women on enzyme-inducing AEDs
- The use of phenytoin, valproate, carbamazepine, lamotrigine, and phenobarbitone has been associated with an increased risk of major malformations and minor morphological anomalies (II)
- Although valproate may the most suitable drug for some women with epilepsy, the risks and benefits should be carefully considered and discussed with the patient (C)
- It is not known whether vigabatrin, gabapentin, levetiracetam, topiramate, oxcarbazepine, pregabalin, and tiagabine are associated with a risk of fetal abnormalities in humans; gabapentin, pregabalin, and tiagabine are not associated with fetal abnormalities in animal studies (III)
- All pregnancies occurring in women with epilepsy should be reported to the appropriate register, regardless of whether or not AEDs are being taken (C)

AED, antiepileptic drug.

Phenobarbitone

Phenobarbitone has been associated with congenital heart defects, facial clefts, and a specific pattern of minor anomalies and dysmorphic features (4).

Valproate sodium

Valproate in pregnancy has been associated with a 1–2% risk of neural tube defects. Some studies have suggested that daily doses of valproate greater than 1,000 mg/day carry a greater risk of spina bifida and other malformations (31,33), possibly due to high peak serum concentrations of valproate. Three or four times daily treatment or slow-release preparations may minimize this risk by reducing peak plasma levels, although the UK pregnancy database has failed to show any benefit of a slow-release formulation (30). There is also an increased incidence of cardiovascular and urogenital malformations (4). Thus, although valproate is a very effective drug for women with generalized epilepsies, the risks and benefits should be carefully considered and discussed with the patient (4).

Carbamazepine

The risk of congenital malformations with carbamazepine monotherapy is similar to that of lamotrigine and phenytoin (30,31). In one study, there was a 0.9% reported risk of neural tube defects in the offspring of mothers who took carbamazepine through pregnancy (4). There have also been reports of reduced head circumference at birth, developmental delay, and dysmorphic features (4).

Lamotrigine

The UK and Australian pregnancy databases currently suggest that the risk of fetal malformations with lamotrigine monotherapy is similar to that of carbamazepine (30,31).

There are not yet enough monotherapy pregnancies with any of the other newer AEDs to be able to accurately advise women, although a recent review of oxcarbazepine does not appear to show an increased risk or any specific pattern of malformations (34). Both topiramate and zonisamide are teratogenic in animal studies.

Although there has been no specific study of the effect of folic acid supplementation on the risk of neural tube defects and other congenital malformations in women taking valproate or other AEDs, extrapolations have been made from published studies in the general population, and therefore a daily dose of 5 mg of folic acid is recommended for all women taking AEDs, starting before conception and continuing until at least the end of the first trimester (4).

Although major malformations associated with AED exposure have been of great concern, minor dysmorphic features in the offspring have been recognized for many years. Dysmorphic features, including epicanthal folds, long philtrum, flat nasal bridge, digital hypoplasia, and hypertelorism, are undesirable and cause some disability but do not result in serious impairment or death. Such abnormalities have been ascribed to syndromes related to specific AEDs, such as the "fetal hydantoin syndrome" and subsequently revised to recognize a "fetal AED syndrome" (1). The extent of the causal relationship with AEDs has been questioned, and evidence has been put forward for maternal genetic factors influencing the development of minor abnormalities such as epicanthus and micrognathia (35). Larger prospective studies of women treated with monotherapy are necessary to resolve these issues. Valproate exposure in utero is associated with a specific combination of facial dysmorphic (36).

Digital and craniofacial hypoplasias tend to resolve over the first few years of life (1). Some investigations have reported that babies exposed to AEDs in utero tend to be small at birth and have slow postnatal growth and cognitive development, but controlled data are lacking. A recent retrospective study has suggested that there may be problems with the later development of children born to mothers receiving valproate sodium therapy or having had more than five tonic–clonic seizures through pregnancy (37); however, most studies have suggested that the risk of prenatal AED exposure leading to low intelligence is low (38).

Genetic predisposition

Many women ask about the risks of passing epilepsy to their children, and the majority can be assured that their child is at low risk. In specific cases, there may be an underlying genetic cause. For idiopathic generalized epilepsy (IGE), the risk of a child developing the condition is 5–20% if there is one affected first-degree relative, and over 25% if two first-degree relatives are affected. Thus, the risk of a woman with IGE having an affected child is about 9–12% (39).

Effect of pregnancy on epilepsy

Many women with epilepsy do not experience an increase in seizures while pregnant. Of those women who do have an increase in seizures (between 8% and 46% in various studies) (40), the increase can often be attributed to factors such as poor compliance with prescribed AEDs (sometimes compounded by vomiting), inappropriate reduction of AED therapy, a pregnancy-related fall in plasma drug concentrations (phenytoin, carbamazepine, phenobarbitone, and lamotrigine), and sleep deprivation (41). There is a debate as to whether AED concentrations should be routinely measured during pregnancy. If they are measured, the unbound level should be measured, because there are changes in protein binding during pregnancy. Alternatively, the patient's seizures should be monitored and AEDs altered accordingly (4). There is no evidence that a nonconvulsive seizure adversely affects a pregnancy or developing fetus apart from the result of trauma (4). Anecdotally, tonic–clonic seizures may cause a fetal bradycardia or miscarriage (4). Tonic–clonic status epilepticus in

TABLE 5. *Management of pregnancy and birth in women with epilepsy—statements and recommendations*

- Most women with epilepsy have normal vaginal deliveries (II)
- Women should be referred by their obstetric/gynecological consultant to a specialist center for high-quality ultrasound (C)
- The patient's seizures should be monitored and appropriate adjustments of AED dosage made (C)
- AED exposure (particularly enzyme-inducing AEDs) leads to greater risk of haemorrhagic disease of the newborn; thus, vitamin KI should be given to the mother in the last month of pregnancy and to the neonate (B)
- Delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation (C)
- The optimal maintenance dose of AEDs should be reviewed after delivery (C)
- All AEDs currently available can be taken while patient is breast feeding (C)
- All women with epilepsy should be encouraged to breastfeed their babies (C)
- If drowsiness occurs in breastfed babies whose mothers are taking phenobarbitone, breast and bottle feeding can be alternated (C)

AED, antiepileptic drug.

pregnancy carries a high mortality for both the mother and fetus (42).

Vitamin K prophylaxis

Hemorrhagic disease of the newborn is more likely to occur in infants whose mothers are taking hepatic microsomal enzyme-inducing AEDs (43). A dose of 20 mg/day of vitamin K should be given daily orally in the last month of pregnancy to these mothers. Infants should receive 1 mg of vitamin K intramuscularly at birth (4).

Management of pregnancy and birth in epilepsy

Most pregnancies are uneventful in women with epilepsy, and most babies are delivered healthy (see Table 5). Recent studies have not indicated any increased risk of obstetric complications in women with epilepsy (44). Older studies suggested that the risk of common complications such as toxaemia, preeclampsia, placental bleeding, and premature labor was approximately three times greater and the risk of perinatal mortality up to two times greater in women with epilepsy (45).

Over breathing, sleep deprivation, pain, and emotional stress increase the risk of seizures during labor, and it is appropriate to consider epidural anesthesia early on. One to two percent of women with active epilepsy will have a tonic–clonic seizure during labor, and a further 1–2% will have a seizure in the following 24 h (46). Generalized tonic–clonic seizures are likely to result in hypoxia, and this may have deleterious effects on the fetus (4). Therefore, the delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation (4). The patient's regular AED should be continued throughout labor. If a corticosteroid is necessary due to premature labor, women taking hepatic microsomal enzyme-inducing AEDs will need an increased corticosteroid dose to try to prevent respiratory distress syndrome in the baby (44,47).

Puerperium

If the dose of an AED has been increased during pregnancy, it is usually advisable to gradually reduce it to the preconception dose over the few weeks following delivery, to reduce the risk of maternal drug toxicity (4).

Breast feeding

All women with epilepsy should be encouraged to breastfeed their babies; however, women with epilepsy are less likely to choose to breastfeed and are more likely to feed for a shorter duration compared with other mothers (48). The AED concentration profiled in breast milk follows the plasma concentration curve, but a delay is often observed. Drug concentrations in milk differ substantially between the first and last portion of the feed. There is also a difference between the left and right breast, depending on the fat and protein content of milk (49,50). The total amount of drug transferred to infants via breast milk is usually much smaller than the amount transferred via the placenta during pregnancy (1,4). However, as drug elimination mechanisms are not fully developed in early infancy, repeated administration of a drug such as lamotrigine via breast milk may lead to accumulation in the infant, and it has been suggested that lamotrigine levels should be monitored in breastfed children whose mothers are taking high-dose lamotrigine (51–53). One study showed 30% infant lamotrigine levels compared with maternal plasma concentrations 2 weeks after delivery (53). Maternal benzodiazepine and barbiturate therapy can cause infant drowsiness. Levetiracetam breast milk concentrations were significantly lower in breast milk compared with maternal blood levels (54). Zonisamide is excreted in breast milk. The concentration in breast milk is similar to maternal plasma (Zonisamide data on file).

The care of children of mothers with epilepsy

Although there is much anxiety about the possible risks to a child from the mother's epilepsy, there is little published evidence. The risk of the child being harmed depends on the type of seizure and its severity and frequency, and this risk is probably small if time is taken to train mothers and caregivers in safety precautions (55). The women most at risk are those with uncontrolled JME, because

TABLE 6. *Epilepsy and the menopause—statements and recommendations*

• The effects of epilepsy on menopause, and the effects of the hormonal changes of menopause and HRT on epilepsy, cannot be reliably predicted (III)
• Women with epilepsy on long-term AED therapy are recognized to be at risk of bone demineralization (I\II)

AED, antiepileptic drug; HRT, hormone replacement therapy.

children tend to wake early, and these mothers are more likely to have myoclonic jerks at that time (55). Advice about safety precautions should be given to mothers (55), even those who have not had a seizure for some time, because it is possible that seizures may return or their frequency increase due to stress, sleep deprivation, and exhaustion in the puerperium.

Menopause

Menopause and its effects on women with epilepsy is an under-researched area (see Table 6). Menopause occurs significantly earlier in women with a high seizure frequency (56). During menopause, about 40% of women report worsening of their seizure disorder, 27% improve, and a third have no change (57). Hormone replacement therapy is significantly associated with an increase in seizure frequency during menopause, and this is more likely in women with a history of catamenial epilepsy (56,58). A randomized study in 21 patients demonstrated a dose rate increase in seizure frequency with hormone replacement therapy (59).

Bone health

Women with epilepsy are at increased risk of fractures, osteoporosis, and osteomalacia. This is multifactorial. There are adverse effects of AEDs on bone metabolism, vitamin D, and bone turnover. There is also the trauma of seizures and subtle effects of AEDs on coordination (55). A recent study in the United States showed that nearly 90% of people with epilepsy took some form of calcium/vitamin D supplement, but only 47% had had dual-energy x-ray absorptiometry scans, due to managed care in the United States (60). The most effective therapy for AED-induced osteoporosis has not been established, but it has been suggested that women on long-term AEDs should have bone density monitored on a regular basis (1).

CONCLUSIONS

Epilepsy and AEDs can affect each aspect of the female human life cycle—menstrual cycle, contraception, fertility, conception, pregnancy, and menopause (including hormone replacement therapy and bone health). These have been discussed under their respective sections in this article. The current level of quality research is limited. Evidence levels for recommendations and therapy have been given where known.

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