Management of epilepsy in women

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Epilepsy is a common neurological condition in women worldwide. Hormonal changes occurring throughout a woman's life can influence and be influenced by seizure mechanisms and antiepileptic drugs, presenting unique management challenges. Effective contraception is particularly important for women with epilepsy of childbearing potential because of antiepileptic drug-related teratogenicity and hormonal interactions; although studies reveal many women do not receive contraceptive and preconceptual counselling. Management challenges in this population include the higher risk of pregnancy complications and peripartum psychiatric problems than in women without epilepsy. Research is needed to clarify the precise role of folic acid supplementation in prevention of congenital malformations in children born to women with epilepsy. To optimise treatment of low bone density in women with epilepsy, studies investigating bone densitometry frequency and calcium and vitamin D supplements are required. Understanding of the mechanisms linking seizures and the menopause will help to develop effective therapeutic strategies, and advances in managing epilepsy could improve quality of life for women with this condition.

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Introduction

Epilepsy is a common neurological condition in women globally, with an estimated prevalence of 6·85 cases per 1000 women.[1] The condition presents unique management challenges in women because hormonal changes throughout a woman's life can affect seizure control, antiepileptic drug metabolism, and vice versa.[2] For example, around a third of women with epilepsy have catamenial epilepsy, defined as seizures occurring at certain times of the menstrual cycle.[3] Research into catamenial epilepsy is progressing, but definitive treatment remains elusive because results have been inconclusive.[3] For example, in a placebo controlled study, the proportion of women with catamenial epilepsy who reported a 50% or greater reduction in their seizure frequency during a 3 months treatment with cyclic progesterone than reported during a 3-month baseline period was not significantly different compared with women with non-catamenial epilepsy.[4]

Contraception[5] and preconceptual counselling[6,7] are particularly important for women with epilepsy because of the potential antiepileptic drug interactions with steroid hormones and potential for teratogenicity (appendix). Antiepileptic drug interactions result in less contraceptive choice for this population[5] and substantially fewer women with epilepsy use hormonal contraception than women without epilepsy.[8] Preconceptual counselling is particularly pertinent if valproate is used because of the evidence regarding neurodevelopmental problems[9,10] and teratogenic effects in the children of mothers taking valproate.[11–15] Despite these issues, many women with epilepsy do not receive adequate contraceptive counselling[16,17] and preconceptual counselling[18] from clinicians, and with UK guidelines[6,7] based on good clinical practice only, robust data are needed to inform optimal management.

Women with epilepsy have poorer pregnancy outcomes than the general population. Morbidity and mortality rates are higher than for women without epilepsy,[19–25] but causes are unclear. Women with epilepsy are also more likely to have an earlier menopause and perimenopause than women without epilepsy, but reasons remain unknown. Research is also required to establish mechanisms underlying bone loss, which is a risk for women receiving antiepileptic drugs. These drugs are associated with a reduction in bone mineral density.[26]

In this Review we examine the latest evidence regarding issues for women with epilepsy. These hormonal aspects, including the menstrual cycle, the influence of antiepileptic drug treatment, and contraception are considered. Previous data regarding fertility, folic acid use, and pregnancy in women with epilepsy are discussed. We also present the minimal body of evidence surrounding menopause in women with epilepsy, as well as considering ways in which research into bone density issues in this patient population might be improved.

Hormonal changes

Female sex steroid hormones can affect neuronal excitability: oestrogens are generally regarded as having an excitatory effect, primarily via excitatory glutamate receptors; while progesterone and its metabolites (primarily allopregnanolone) exert an inhibitory effect via postsynaptic inhibitory GABA-A receptors.[27] Therefore, hormonal fluctuations throughout the menstrual cycle could affect seizure control.[28]

Menstrual cycle

Variation of seizure frequency across the menstrual cycle, affecting around a third of women, is referred to as catamenial epilepsy.[3] Catamenial epilepsy generally manifests as worsening seizure frequency around menstruation, although seizures might also occur before ovulation and during anovulatory cycles with inadequate luteal phases.[28] Research has mainly focused on the premise that premenstrual lowering of progesterone concentrations is implicated in catamenial seizures.[28] However, a randomised (2:1), double blind, placebo-controlled study of an adjunctive natural progesterone supplement versus placebo showed no statistically significant difference in the proportion of patients who reported a 50% or greater reduction in seizure frequency, between 130 women with catamenial epilepsy and 164 without catamenial epilepsy.[4]

See Online for appendix

The similar response between these two groups might have occurred because not all catamenial seizures occur around menstruation, manifesting at other cycle stages when endogenous progesterone concentrations are perhaps not implicated. In a subanalysis of 63 of the worst-affected women who had a 3-fold increase in perimenstrual seizure frequency compared with midfollicular and midluteal phases, a statistically significant increase in the proportion of responders with a progesterone supplement was reported (n=24, 37·8%) than was observed with placebo (n=7, 11·1%). In a post hoc analysis, the authors postulated that allopregnenalone, the main metabolite of progesterone, might have reduced seizure frequency in these women, given the statistically significant rise in allopregnenalone concentrations between baseline and treatment cycles.[29] However, these findings require validation in a larger, more robust study. When catamenial epilepsy is suspected, a diary can help establish a seizure pattern. In patients with irregular menstruation, oral hormones can aid cycle regulation, with the aim of rendering seizures more predictable. Antiepileptic drug-regimen optimisation might reduce seizures, but no robust evidence exists regarding antiepileptic drug efficacy. In a small, double-blind, crossover study of 18 women with menstrual seizures, 14 (78%) had improved seizure control with clobazam, with a 10-day treatment period starting 2–7 days before the predicted day of menstruation, or seizure onset.[3] Despite clobazam being widely used in everyday clinical practice for women with catamenial seizure patterns, no robust efficacy data for this has been shown, or for any other antiepileptic drug.Such studies would be welcome, as would research into the mechanisms, hormonal or otherwise, underlying catamenial epilepsy.

Antiepileptic drugs

Antiepileptic drugs can be associated with sexual dysfunction in women. Enzyme-inducing antiepileptic drugs, particularly carbamazepine, phenytoin, phenobarbital, and oxcarbazepine might reduce libido through low concentrations of total serum testosterone, free androgen index, dehydroepiandrosterone sulphate, and oestradiol, and increased concentrations of sex hormone binding globulin.[30] Topiramate[31] and gabapentin[30] have been associated with anorgasmia in anecdotal and questionnaire-based reports. However, women who adhere to and achieve good seizure control with antiepileptic drugs might have improved sexual functioning[32] because of a reduction in anxiety and improved quality of life, both of which were positively correlated with antiepileptic drug adherence in a 9-month prospective study of 567 Iranian women with epilepsy.[32] Note that only a minority of neurologists working in out-patient clinics asked their patients with epilepsy about libido, as reported in a Norwegian questionnaire study.[33] Future case-control studies might provide information on the role of iatrogenic effects and the effect of seizures on psychological symptoms in women with epilepsy.

Hepatic enzyme-inducing antiepileptic drugs, such as carbamazepine and phenytoin, can affect hormones such as thyroxine and triiodothyronine in women and men.[34] For example, a meta-analysis of 35 cross-sectional, case-control, and cohort studies evaluating the association between antiepileptic drugs and thyroid hormones found that patients with epilepsy receiving antiepileptic drugs had a reduction in thyroxine (T_4), free T_4, and high thyroid stimulating hormone concentrations compared with healthy controls.[34] However, those patients did not generally develop hyperthyroidism,[34] suggesting thyroid function monitoring is not routinely required.

Valproate has been found to inhibit hepatic cytochrome P450 isoenzymes and adversely affected sexual and thyroid function.[34] Valproate is associated with hyperandrogenism, insulin resistance, weight gain, polycystic ovaries and polycystic ovarian syndrome, menstrual disorders, ovulatory failure, and infertility in women.[35] Valproate should therefore be avoided, if possible, in women of childbearing potential. When valproate use is necessary to control seizures, relevant signs and symptoms should be enquired about regularly by managing clinicians, with referral for a gynaecological opinion if necessary.

Contraception

Effective contraception for women of childbearing potential is paramount as many antiepileptic drugs have teratogenic potential[15] and interact with steroid hormones (table 1, appendix).[5] However, data suggest hormonal contraception use is low in this population compared with women without epilepsy.[8] For example, a Norwegian population-based study of pregnant women, consisting of 129 women with epilepsy and 20 897 controls (women without epilepsy), aged 15–44 years, showed only 25 (19%) women with epilepsy used hormonal contraception compared with 5474 (26%) women without epilepsy.[8] Contraception use was particularly low in women with epilepsy aged younger than age 25 years (nine [17%] of 52) compared with age-matched controls (1535 [35%] of 4449).[8] Clinicians might not enquire about contraceptive use. Two retrospective, observational studies of women of childbearing potential taking antiepileptic drugs for epilepsy revealed that only 30 (26%) of 115 women[16] and 272 (69%) of 397 women[17] had their contraceptive methods documented. UK guidelines[6,7] recommend that contraceptive advice should ideally be given before a woman with epilepsy becomes sexually active, and reviewed on a regular basis. Written handouts, given to patients, can aid information retention.[36]

Fertility

Information regarding fertility in women with epilepsy is scarce. A Norwegian database study of more than 25 000 pregnant women showed similar birth numbers per 1000 women for women aged younger than 20 years with and without epilepsy; however, birth numbers were significantly lower for women between 25 and 35 years

	Carbamazepine	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Topiramate	Valproate
International Registry of Antiepileptic Drugs and Pregnancy[15]	5·5% (107/1957)	2·9% (74/2514)	2·8% (17/599)	3·0% (10/333)	6·5% (19/294)	6·4% (8/125)	3·9% (6/152)	10·3% (142/1381)
North American Antiepileptic Drugs Pregnancy Registry[11]	3·0% (31/1033)	2·0% (31/1562)	2·4% (11/450)	2·2% (4/182)	5·5% (11/199)	2·9% (12/416)	4·2% (15/359)	9·3% (30/323)
UK Epilepsy and Pregnancy Register[12]	2·6% (43/1657)	2·3% (49/2098)	0·7% (2/304)	NA	NA	3·7% (3/82)	4·3% (3/70)	6·7% (82/1220)

NA=not available.

Table 1: **Prevalence of congenital malformations for different antiepileptic drug monotherapies**

with epilepsy compared with those without epilepsy.[8] Although the study results could indicate participants' fecundity, the outcomes might also be a reflection of the broad population of women with epilepsy included in the database who were not necessarily trying to become pregnant, or for whom psychosocial circumstances such as difficulties in finding a partner, low self-esteem, and social isolation, influenced becoming pregnant. Encouraging results were reported in a US prospective, observational study of 89 women with epilepsy and 108 controls without epilepsy aiming for pregnancy.[37] 54 (61%) women with epilepsy achieved a pregnancy within 12 months of enrolment, which was similar to the proportion of women in the control group (65 [60%]) who became pregnant. The median time to pregnancy was also similar in both groups at 6 months (95% CI 3·8–10·1) and 9 months (95% CI 6·5–11·2) respectively, as was the number of live births (45 [81·5%] of 54 pregnancies for women with epilepsy; 53 [81·5%] of 65 pregnancies for women without epilepsy).[37]

A retrospective study found that epilepsy surgery in the form of focal cortical resection had a positive effect on fertility in 113 women aged 18–45 years, with drug-resistant focal epilepsy followed up, on average, for 5·7 years postoperatively.[38] The mean number of preoperative pregnancies per woman was 0·93 (increasing to 1·27 postoperatively), and for preoperative births was 0·73 (increasing to 0·96 postoperatively).[38] Prospective, randomised, controlled studies investigating fertility in women with epilepsy are needed to provide data to inform counselling. For women having difficulties conceiving, timely referrals for investigation are warranted.

Preconceptual counselling

Women with epilepsy must consider many more potential pregnancy and childbirth issues than women without epilepsy: these include seizure control, antiepileptic drug teratogenicity, and folic acid supplementation (appendix). Preconceptual counselling for this population is recommended[6,7] and is often undertaken by epilepsy specialist nurses who fulfil a pivotal role in the management of women with epilepsy. Unplanned pregnancies in these patients are common—of 1144 women with epilepsy registered with a US epilepsy birth registry, 437 reported pregnancies occurring after the onset of their seizures. Of the 437 women, 345 (78·9%) reported at least one unintended pregnancy.[39] As a comparison, the prevalence of unintended pregnancies in the USA has been found to be 2·8 million (45%) of 6·1 million pregnancies.[40] In an American pregnancy risk assessment monitoring sample, 299 (55%) of 548 women with epilepsy reported unintended pregnancies compared with 35 042 (48%) of 73 619 women without epilepsy.[41] Antiepileptic drug adherence can be an issue during pregnancy for some women with epilepsy. Of 160 pregnant women with epilepsy participating in an international online questionnaire, 64 (40%) reported antiepileptic drug adherence problems.[42] Current preconceptual counselling seems inadequate for many women with epilepsy based on a meta-analysis[18] of 12 studies that used quantitative methods to evaluate knowledge, needs, and concerns: women reported adequate awareness, but inadequate knowledge of key pregnancy and birth issues. These findings emphasise the importance of regular preconceptual counselling for women of childbearing potential with epilepsy (appendix).

Folic acid

Women with epilepsy are at increased risk of giving birth to children with congenital malformations.[43,44] Although evidence for congenital malformation prevention with folic acid use is inconclusive in this population, the supplement is associated with neurodevelopmental benefits.[45–47] For example, a Norwegian population-based biobank study[47] showed that of 328 children born to mothers with antiepileptic drug-treated epilepsy, those not exposed to folic acid (n=68, 20·7%) had a significantly higher risk of autistic traits (5–8 times) at 18 months and 36 months, compared with those whose mothers had taken folic acid (n=260, 79·3%). The degree of autistic traits was inversely associated with maternal plasma folate concentrations and folic acid doses.[47] Data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study[45] of 305 pregnant women with epilepsy receiving antiepileptic drug monotherapy showed that mean intelligence quotients (IQs) were higher in 108 (35%) children exposed to periconceptual folate than the IQs of 101 (33%) non-exposed children.[45] However, this outcome did not occur in a later analysis from the same cohort, but the cause for the discrepancy remains unclear.[46] Note that the studies did not provide details of dose, timing, or duration of folic acid use, making

Panel: **Case study of health problems in a woman with epilepsy**

An 11-year-old girl presented with a generalised tonic-clonic seizure and a 1-year history of staring episodes lasting less than 1 min. These episodes were consistent with absence seizures, and a routine, interictal EEG showed regular 3 Hz spike, polyspike, and wave complexes. An MRI brain scan was normal and she was otherwise healthy with no risk factors. A genetic generalised epilepsy was diagnosed and seizures reduced with lamotrigine. At age 15 years, levetiracetam was added to control myoclonic jerks, but was discontinued because of sedation. The lamotrigine dose was increased to 400 mg daily. At age 17 years, absence seizures worsened, coinciding with the prescription of a levonorgestrel and norethisterone oral contraceptive pill, which might have reduced circulating lamotrigine concentrations. A desogestrel pill was substituted in the hope that the progesterone would have an anticonvulsant effect. Following further generalised tonic-clonic seizures and after preconceptual and antiepileptic drug counselling, sodium valproate was substituted for lamotrigine—absences, but not myoclonic seizures, were abolished with 2000 mg sodium valproate daily. Because of fatigue, the sodium valproate dose was reduced to 1200 mg daily and zonisamide 100 mg daily was added. At age 21 years, the sodium valproate dose was decreased to 500 mg daily to lessen teratogenic potential. However, the generalised tonic-clonic seizures returned despite zonisamide dosing being increased to 400 mg daily. Sleep deprivation, alcohol misuse, and adherence problems were precipitating factors. After further preconceptual counselling, sodium valproate 800 mg daily lessened the frequency of generalised tonic-clonic seizures. At age 23 years, the patient began cognitive behavioural therapy for depression. Although a zonisamide dose reduction was suggested, she increased her dose and has been seizure-free for 1 year, receiving 400 mg daily with sodium valproate 800 mg daily. At her last consultation she was counselled regarding sodium valproate European Medicines Authority (EMA) recommendations and the pregnancy prevention programme.[53] To fulfil EMA criteria, she will need to alter her contraceptive regimen or discontinue sodium valproate.

interpretation of the results difficult. However, although evidence is inconclusive, UK guidelines[6,7] recommend folic acid supplementation. Optimal dosing remains a subject of debate, but at least 400 mcg daily, and up to 5 mg daily is recommended as a preconceptual dose and for at least the first trimester.[7]

Valproate

Given its teratogenic potential, restrictions on valproate use in women of childbearing potential with epilepsy, issued by the US Food and Drug Administration[48] and the European Medicines Agency (EMA)[49] have been enforced. Patients in Europe taking valproate are recommended to fulfil EMA pregnancy prevention programme requirements.[49] The programme requires assessment of pregnancy potential, pregnancy testing before and during valproate treatment if required, counselling about the risks of valproate and effective contraception, completion of a risk acknowledgment form by the patient and prescriber, and annual review of the need for valproate.

As valproate has been used as the drug of first choice for many women with genetic generalised and unclassified epilepsies[50] who might achieve seizure control with low dosing, these restrictions create a dilemma for clinicians and patients. A comprehensive assessment and discussion of options can aid decision making.[51] Counselling should cover not only the adverse and beneficial effects associated with valproate, but also the risks of continued seizures with a potentially less efficacious antiepileptic drug (panel).[52]

Pregnancy

Epilepsy is one of the most common neurological disorders in pregnancy, with a prevalence of 0·3–0·7%.[19] Given the ethical and practical challenges of regulatory studies in pregnant women with epilepsy, registry data have been pivotal to informing management decisions.[11,12,54]

Seizure control

During pregnancy, the majority of women with epilepsy, including those with catamenial epilepsy,[55] have an improvement in seizures or remain seizure-free.[54,55] For example, of 3806 pregnancies in 3451 women with epilepsy enrolled in the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP),[54] 2521 (66%) pregnancies were seizure-free. Seizure freedom occurred in 1096 (73·6%) of 1491 pregnancies in 1356 women with genetic generalised epilepsies. Significantly fewer of the 1607 women with localisation-related epilepsies were seizure free—1063 (59·5%) of 1786 pregnancies. Seizure control in the second and third trimesters was compared with that of the first trimester in 3735 women. Of these pregnancies, seizure control deteriorated in 589 (15·8%).

Valproate (546 [75%] of 728) and phenobarbital (114 [73%] of 157) were associated with the highest number of seizure-free pregnancies, perhaps because these antiepileptic drugs have efficacy for a wide range of seizure types and syndromes.[50] A lower percentage of pregnant women exposed to carbamazepine (914 [67%] of 1359) and lamotrigine (722 [58%] of 1240) were seizure free than those exposed to valproate (728 [75%] of 971) and phenobarbital (157 [73%] of 214).[54] Lamotrigine concentrations fall precipitously in pregnancy and it is possible that lower concentrations might have resulted in a deterioration of seizure control for some women.[56]

EURAP data analysis revealed a much higher status epilepticus incidence (21 [0·6%] of 3451 women) during pregnancy[54] than in the general population (0·013% [12·6 per 100 000 men and women with epilepsy]).[57] This increased incidence might be because of variations in

reporting methods or data collection, or could reflect an actual increased incidence in pregnant women with epilepsy. Further studies of status epilepticus incidence in pregnant and non-pregnant women with identical methodology are required to further examine these findings.

A US retrospective hospital record study showed increased mortality in pregnancy for women with epilepsy (80 deaths per 100 000 pregnancies) compared with those without the condition (6 deaths per 100 000 pregnancies).[19] In the UK, epilepsy remains one of the leading indirect causes of maternal death, with sudden unexpected death in epilepsy being the commonest cause.[20,21] Thus, for pregnant women with uncontrolled seizures, every effort should be made to optimise seizure control and provide counselling and support.[7]

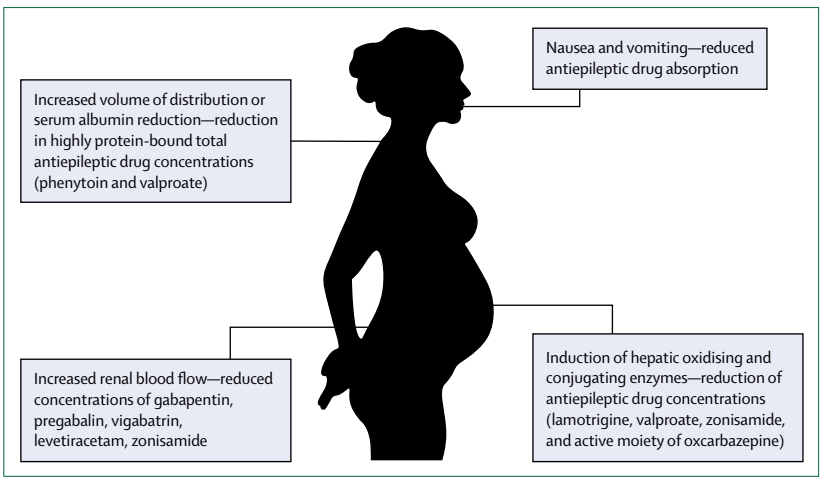

Figure: **Alterations in antiepileptic drug metabolism in pregnant women with epilepsy**

Antiepileptic drug metabolism

Physiological changes during pregnancy affect antiepileptic drug absorption, distribution, metabolism, and excretion (figure).[58] Circulating concentrations of lamotrigine,[56] levetiracetam,[56] topiramate,[59] zonisamide,[53] and oxcarbazepine[56] can fall as pregnancy progresses.[56] Fetal gender and genetic polymorphisms of uridine diphosphate-glucuronosyltransferase (UGT), via which lamotrigine is largely metabolised, might affect lamotrigine concentrations.[60] A retrospective study[60] of 47 pregnancies in 40 women with epilepsy found that those carrying a female fetus had significantly higher reductions in lamotrigine concentration to dose (C:D) ratios than those carrying a male fetus. Women with the *UGT1A4 142TG (*3)* polymorphism had a significantly less pronounced decrease in lamotrigine C:D ratios in the third trimester than those with the wild-type.[60] Homozygous carriers of UGT2B7 802TT had significantly lower C:D ratios in the first and third trimester than heterozygous carriers.[59] Therapeutic drug monitoring can aid antiepileptic drug dose manipulation during pregnancy.[60] Although robust evidence is not available, a UK guideline[7] recommends that antiepileptic drugs should be continued throughout pregnancy and lactation to attain seizure freedom whenever possible and prevent tonic-clonic seizures.

Valproate is associated with the highest risk for congenital malformation (table 1).[11,12,15] The risk is dose-related, heightening when dose increases from 500 mg to 750 mg daily.[11,12,15] Genetic factors, such as a family history of neural tube defects, or individual susceptibility, might also be implicated in the production of congenital malformations.[61] Valproate use during pregnancy has been associated with poorer neurodevelopmental outcome in offspring,[9,62] with more children showing cognitive, psychomotor, or language developmental delays, than children of untreated women with epilepsy.[14] A significantly lower IQ (mean score 97) was found in children of women receiving valproate than in those taking carbamazepine (IQ 105), lamotrigine (IQ 108), or phenytoin (IQ 108).[45,63] Additionally, children exposed to higher valproate doses (>800mg/day) had an adjusted mean IQ 9.7 points lower (95% CI –4.9 to –4.6; p<0.001), as well as significantly poorer outcomes for verbal, non-verbal, and spatial subscales; and an 8-fold increased need of educational intervention compared with children of mothers without epilepsy, suggesting a dose-dependent association.[64] Compared with children born to women without epilepsy, children of mothers with epilepsy receiving valproate or multiple antiepileptic drugs during pregnancy had lower attainment scores at ages 7–16 years in Welsh national tests for mathematics and science, but not languages.[65] Furthermore, valproate exposure in utero was associated with increased risk of autism spectrum disorder, dyspraxia, and attention-deficit hyperactivity disorder in offspring.[14,66,67] Valproate should therefore be avoided, when possible, in women of childbearing potential.

Pregnancy complications

When counselling a pregnant or prepregnant woman with epilepsy, informing them that the majority of women with epilepsy will have a straightforward pregnancy, delivery, and give birth to a healthy baby is essential.[22] An increased risk of pregnancy complications was shown in several studies of women with epilepsy, although these were retrospective in nature and provided an insight into morbidity and mortality, information on underlying causes was not elucidated (table 2),[19,22,24,25] particularly for a first pregnancy.[68] Pregnancy register data[69] also showed that spontaneous abortions were significantly higher in antiepileptic drug-exposed women, including those with epilepsy, than in women not taking antiepileptic drugs or those without epilepsy. Furthermore, termination of pregnancy was significantly more likely in women receiving antiepileptic drugs than those not receiving antiepileptic drugs.[70]

The prevalence of pre-eclampsia was higher in women with epilepsy than in women without epilepsy.[71] Although fewer women were prescribed valproate than were

	MacDonald et al (2015)[19]	Razaz et al (2017)[24]	Artama et al (2017)[22]	Soonturnupun et al (2018)[25]
Study details	US hospital record-based study; 69 385 women with epilepsy and 20 449 532 controls*	Swedish registry-based study; 3586 women with epilepsy and 869 947 controls	Finnish health register and population statistic study; 1737 women with epilepsy and 4357 controls	Thai database single-centre study; 148 women with epilepsy and 1480 controls
Caesarean section	1·40 (1·38–1·42)	NA	1·25 (1·11–1·41)	RR 1·50 (1·10–2·10)
Elective caesarean section	NA	1·58 (1·45–1·71)	1·53 (1·25–1·88)	NA
Emergency caesarean section	NA	1·09 (1·00–1·20)	NA	NA
Induction of labour	1·14 (1·12–1·16)	1·31 (1·21–1·40)	1·23 (1·08–1·41)	RR 1·20 (0·70–1·90)
Gestational hypertension	0·96 (0·92–1·00)	NA	1·09 (0·79–1·51)	NA
Pre-eclampsia	1·59 (1·54–1·63)	1·24 (1·07–1·43)	1·23 (0·91–1·66)	RR 0·90 (0·40–1·70)
Post-partum haemorrhage	1·14 (1·08–1·20)	1·11 (0·97–1·26)	0·96 (0·71–1·28)	RR 1·30 (0·70–2·70)
Antepartum haemorrhage	1·38 (1·31–1·45)	NA	1·25 (0·83–1·89)	RR 1·10 (0·40–3·00)
Gestational diabetes	1·11 (1·07–1·15)	0·94 (0·55–1·59)	1·09 (0·79–1·51)	NA
Infection	NA	1·33 (0·66–2·65)	0·87 (0·49–1·53)	NA
Placental abruption	NA	1·68 (1·18–2·38)	NA	NA
Preterm labour	1·50 (1·50–1·57)	NA	NA	RR 1·60 (1·10–2·30)
Premature rupture of membranes	1·07 (1·03–1·11)	1·20 (0·98–1·48)	1·75 (1·14–2·69)	NA
Chorioamnionitis	1·17 (1·11–1·23)	1·44 (0·87–2·39)	NA	NA
Stillbirth	NA	1·55 (1·05–2·30)	1·00 (1·00–1·00)	RR 0·40 (0·60–3·00)
Preterm birth	1·54 (1·50–1·57)	1·49 (1·34–1·66)	<34 weeks 1·32 (0·84–2·09); ≤34 weeks 1·29 (0·99–1·68)	RR 1·60 (1·10–2·30)
Post-term birth	NA	NA	0·98 (0·96–1·00)	NA

Data are ARR (95% CI). ARR=adjusted risk ratio. NA=not available. RR=risk ratio. *Controls from a US community hospital stratified sample.

Table 2: **Pregnancy complications in women with epilepsy**

prescribed other drugs, the proportion of women with pre-eclampsia was higher with valproate than with lamotrigine or levetiracetam.[71] Data from 706 women registered with the Norwegian Mother and Child Cohort Study (MoBa) study[72] found a higher prevalence of pre-eclampsia in women with epilepsy and eating disorders than those without epilepsy or eating disorders. Clinicians should be aware that in women with epilepsy, eating disorders can be associated with complications in pregnancy. These issues should be raised during pre-conceptual counselling and referral for management of affected women prior to pregnancy could help avert problems during pregnancy.

Obesity was more common in pregnant women with epilepsy than those without epilepsy, conferring an increased risk of caesarean section and excessive bleeding compared with overweight controls without epilepsy and women with epilepsy of normal body-mass index.[73] Given the increased risk for delivery complications, women with epilepsy should have consultant-led obstetric care and delivery, and should be admitted to hospital should complications arise.[7]

Postnatal management

The postnatal period can be a difficult time for a woman with epilepsy. Although UK clinical guidelines[6,7] recommend assured, repeated contact with clinicians following the birth, robust evidence for management strategies is absent (appendix). After the birth, antiepileptic drug concentrations increase as the physiological changes of pregnancy reverse.[74] If antiepileptic drug dosing was increased during pregnancy, dosage reduction will be required post partum to prevent toxicity. If feasible, concentration monitoring can provide guidance on antiepileptic drug dosing.[74] Postnatal depression and anxiety might require pharmacological or psychological treatment.[75] Breastfeeding problems and physical health issues, which can adversely affect maternal mood,[76] need to be identified and managed appropriately.

Peripartum psychiatric comorbidities

Anxiety and depression are substantial issues for women with epilepsy in the peripartum period.[75] During pregnancy and up to 36 months postnatally, anxiety and depression questionnaires were completed by 706 women with epilepsy participating in the MoBa study.[77] Compared with 106 511 women without epilepsy and 8372 with other chronic diseases (including prepregnancy hypertension; asthma; renal, heart, or thyroid diseases), those with epilepsy more often had depression or anxiety, but were less likely to receive antidepressants.[77] A history of anxiety, depression, and antiepileptic drug treatment conferred greater risk. Physical and sexual abuse, and prepregnancy anxiety and depression negatively affected recovery from anxiety and depression.[77] Epilepsy was also associated with a significantly increased prevalence of binge eating

disorder and impaired body image during pregnancy.[72] Peripartum quality of life information from the MoBa database was examined in 719 women with epilepsy and 101 546 women without epilepsy.[78] Epilepsy was associated with lower global life satisfaction scores, poor self-esteem, and adverse socioeconomic circumstances such as single parenting, financial hardship, low education, and unemployment during and after pregnancy.[78] Given that psychiatric symptoms are common in women with epilepsy during the peripartum period, and that depression, in particular, can be associated with stigma[79] and poorer quality of life[80] in people with epilepsy, clinicians should have a high awareness with prompt liaison with psychiatric services when necessary.

Breastfeeding

The safety of breastfeeding while receiving antiepileptic drugs is a source of major concern for many women with epilepsy, and fewer women with epilepsy breastfeed than those without epilepsy.[81] The NEAD study[81] reported that 78 (43%) of 181 children born to women with epilepsy were breastfed for a mean duration of 7·2 months (95% CI 6·2–8·3 months). These results were similar to those reported in southwest China where a questionnaire-based study of 281 mothers with epilepsy reported 167 (59%) breastfed at birth, decreasing to 139 (49%) at 3 months.[82] Given that these studies were undertaken in populations that vary in many aspects, including culture, health care, and politics, these similar outcomes are interesting.

When counselling a pregnant woman with epilepsy, the clinician should explain that lipid soluble antiepileptic drugs are present in breastmilk, although mostly not in sufficient quantity to produce unwanted effects.[83] However, breastmilk concentrations of barbiturates, benzodiazepines, lamotrigine, zonisamide, and ethosuximide can be elevated, leading to unwanted effects (eg, lethargy and irritability).[83] Sedative drugs, such as phenobarbital, have the potential to induce infant sedation and interfere with breastfeeding.[83] Women should therefore be advised to monitor their infants for side-effects.[83]

Two prospective studies have examined longitudinal outcomes in breastfed children of women with epilepsy.[81,84] MoBa data revealed no adverse effects on motor and social skills, language, and behaviour in children born to parents with epilepsy taking carbamazepine, lamotrigine, or valproate individually or with other antiepileptic drugs, compared with children born to parents without epilepsy.[84] Maternal antiepileptic drug use did not adversely affect child development, and breastfeeding was associated with less impaired development at 6 months and 18 months than those not breastfed or those breastfed for less than 6 months.[84] Valproate was the least used antiepileptic drug, which might account for these positive outcomes. NEAD[81] data showed no adverse effects of breastfeeding at ages 3 years and 6 years when differential ability scales, IQ, verbal and non-verbal memory, and executive functions were measured in 181 children of women with epilepsy receiving phenytoin, carbamazepine, valproate, or lamotrigine. Given these positive outcomes, clinicians should encourage women with epilepsy to breastfeed.

Menopause

Few data are available on epilepsy and the menopause. Two questionnaire-based studies[3,85] showed that women with epilepsy are susceptible to early perimenopause and menopause,[3] with one suggesting an association between greater lifetime seizure frequency and earlier menopause, as much as 3–4 years earlier than expected, for women who had more than 20 seizures.[3] Lower concentrations of antimüllerian hormone, a direct measure of ovarian reserve, were reported in women with epilepsy of reproductive age with seizures than those who were seizure-free.[85] Women with epilepsy should be counselled regarding the implications of early menopause, including a potentially shorter fertility window. When menopause occurs, contraception discontinuation and bone health issues become relevant.

During perimenopause, seizure frequency might increase secondary to rapid changes in oestrogen and progesterone concentrations.[86] At menopause, a seizure reduction can occur, perhaps due to higher concentrations of oestrone, which have been shown to reduce seizures in patients with catamenial epilepsy as well as experimental models. 11 (69%) of 16 women with a history of catamenial seizure exacerbation reported a decrease in seizure frequency in a questionnaire study.[86] These findings suggest endogenous sex steroid hormone variations influence brain excitability in these women. Current management strategies focus on optimisation of antiepileptic drug regimens, but as understanding of the role of hormones in effecting seizures around menopause improves, this might lead to improved therapies for women with epilepsy at this time of life.

Exogenous hormones might also affect seizures in menopausal women with epilepsy.[86] Of 15 women with epilepsy who participated in a randomised, placebo-controlled study of conjugated equine oestrogens with medroxyprogesterone acetate as hormone replacement therapy, six (40%) had a dose-associated increase in seizure frequency and severity compared with those who received placebo.[86] Therefore, hormone replacement therapy should therefore be avoided. Lamotrigine concentrations are reduced by the co-administration of oestrogen-containing hormone replacement therapy[87] and lamotrigine concentration monitoring could be useful for women with epilepsy receiving this drug, as the dosage might need to be increased if seizure control worsens.

Bone density

During the menopause bone turnover increases and bone loss is accelerated, leading to reduced bone mineral

Search strategy and selection criteria

We searched the following databases via the National Health Service Scotland Knowledge Network for articles published in English between Jan 1, 2013, and Nov 6, 2018: Cochrane Epilepsy Group Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, Embase, PsycINFO, CINAHL Plus, Education Resources Information Center, Health Management Information Consortium, Midwives Information and Resource Service, and Books@Ovid. We also searched Scopus, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform. We also searched for non-English publications via the Neurology Asia website, the Neurology India website, the World Federation of Neurology Latin-America Initiative website, and the International League Against Epilepsy website, using the following MeSH terms for specific topics:

- For hormonal changes and menstrual cycle: "epilepsy and women", "seizures and women", "epilepsy and hormones", "seizures and hormones", "epilepsy and menstrual cycle", "catamenial epilepsy", and "catamenial seizures"
- For antiepileptic drug treatment: "antiepileptic drugs and women", "epilepsy and female", "seizures and female", "antiepileptic drugs and female", "antiepileptic drugs and side effects", "antiepileptic drugs and adverse effects", "epilepsy and fertility", "epilepsy and neuroendocrine", "seizures and neuroendocrine", "epilepsy and endocrine"; "seizures and endocrine", "epilepsy and sexuality", and "seizures and sexuality"
- For contraception: "epilepsy and contraception" and "seizures and contraception"
- For fertility: "epilepsy and fertility"
- For preconceptual counselling and folic acid: "epilepsy and preconceptual counselling"; "epilepsy and folic acid"; "antiepileptic drugs and folic acid"; and "valproate and folic acid"
- For pregnancy: "epilepsy and pregnancy", "epilepsy and teratogenicity", "antiepileptic drugs and teratogenicity", "antiepileptic drugs and pregnancy", "epilepsy and mortality", "epilepsy and morbidity", and "pregnancy and mortality"
- For postnatal management: "epilepsy and postpartum", "epilepsy and postnatal", "epilepsy and breastfeeding", "antiepileptic drugs and breastfeeding", "epilepsy and stigma", and "epilepsy and quality of life"
- For menopause and bone density: "epilepsy and menopause", "seizures and menopause", "seizure control and menopause", "epilepsy and bone density", and "antiepileptic drugs and bone density".

Because of the volume of publications available, the decision was made to include only studies with 100 cases or more, unless the paper was considered pivotal to the Review, or no such studies existed for a specific topic.

density.[88] Resultant fractures can lead to chronic pain, disability, and death.[88] As antiepileptic drug use, particularly hepatic enzyme-inducing antiepileptic drugs,[89] is associated with low bone mineral density, this correlation renders postmenopausal women with epilepsy particularly susceptible to fractures.[26] Reasons remain unclear and are likely to be multifactorial (appendix). Poor mobility and intellectual disability confer added risk of reduced bone mineral density.[90] Bone loss can begin before the menopause in some women receiving antiepileptic drugs.[91] For example, a UK general practice register analysis found that for every 10 000 women with epilepsy (median age 48·2 years) who took enzyme-inducing antiepileptic drugs for 1 year, 48 additional fractures occurred.[91] However, other antiepileptic drugs, such as valproate, have been associated with reduced bone mineral density.[92] For example, 50 adults with epilepsy receiving valproate had significantly lower bone mineral density than these without epilepsy.[92]

Management of low bone mineral density in women with epilepsy is complex. Some women might require enzyme-inducing antiepileptic drugs to prevent seizures and changing to another drug with perhaps less risk of reduced bone mineral density might result in a seizure-related fracture. A UK clinical guideline[88] advises bone densitometry screening, but no robust data are available regarding frequency or minimum screening age. A meta-analysis of 479 men and women with epilepsy concluded that vitamin D supplements are beneficial, although dosing is not yet clearly defined.[93] Daily doses of 800 IU have been suggested in combination with calcium, and 1800–4000 IU when used alone.[93] Long-term bone densitometry trials with varying doses of vitamin D and calcium are required to better inform clinical practice.

Conclusions and future directions

Women with epilepsy face many difficult issues at different life stages, with younger women often requiring counselling about seizures and the menstrual cycle, contraception, fertility, and pregnancy. More mature individuals might need advice regarding seizures and the menopause and the association between antiepileptic drugs and bone mineral density.

The mechanisms underlying catamenial epilepsy remain to be elucidated, although research suggests progesterone supplements are not appropriate for most women with the condition.[4] Women with epilepsy report inadequate knowledge of key pregnancy and birth issues, and the use of hormonal contraception is low in this population compared with women in general,[8] suggesting that contraceptive[16,17] and preconceptual[18] counselling for many women with epilepsy could be improved.[8]

Although the majority of women with epilepsy have favourable pregnancy outcomes,[22] research shows higher morbidity and mortality than for pregnant women without epilepsy.[19,20,22–25] Physiological changes during pregnancy alter antiepileptic drug pharmacokinetics

and doses—lamotrigine, levetiracetam, topiramate,[59] zonisamide,[53] and oxcarbazepine[56] doses in particular should be increased. Data show maternal folic acid supplementation confers neurodevelopmental benefits for children of women with epilepsy,[45–47] but potential for congenital malformation prevention and optimum dosing requires further clarification. During the peripartum period, women with epilepsy are significantly more likely to have psychiatric comorbidities than those without epilepsy.[75] Postnatal counselling is therefore vital,[6,7] also allowing breastfeeding, seizure control, and antiepileptic drug issues to be addressed, although evidence for management strategies is scarce.

Early perimenopause and menopause are more common in women with epilepsy than in women without epilepsy,[3] but the underlying reasons remain to be elucidated. Bone loss is a risk for women receiving antiepileptic drugs as they are associated with a reduction in bone mineral density;[26] however, a robust evidence base is required to inform optimal management. Epilepsy also adversely affects a woman's social skills,[94] relationships,[95,96] and employment,[96,97] but underlying mechanisms and corrective measures have not yet been established.

With so many questions remaining unanswered, multiple avenues exist for future research. Identification of which mechanisms lead to catamenial epilepsy will advance the search for a definitive treatment. Development of effective contraceptives, which are non-hormonal or have no drug interactions, will widen choice and might lead to more use and fewer unplanned pregnancies for women with epilepsy. Mechanistic and genetic studies exploring the causes of antiepileptic drug-related congenital malformations and neurodevelopmental abnormalities in children will allow more informed preconceptual counselling for women with epilepsy. If pregnancy outcomes are to be improved in this population, the need to establish the reasons for increased morbidity and mortality is urgent, including reasons for peripartum psychiatric diagnoses. Finally, longitudinal studies focusing on perimenopausal and menopausal seizure patterns, hormone replacement therapy use, and bone mineral density in women with epilepsy will provide useful data to improve management of the condition.

Contributors

LJS wrote the abstract, introduction, hormonal changes, menstrual cycle, contraception, fertility, preconceptual counselling (with MJB and TT), folic acid, valproate (with MJB and TT), pregnancy (including seizure control, antiepileptic drug therapy, and delivery complications with MJB), postnatal management and breastfeeding (with MJB), bone density (with CH), conclusions and future directions, tables 1 and 2 and figure 1 in the main text, and figure 2 in the appendix. CH wrote menopause and bone density. TT also made contributions to table 1 and gave manuscript advice.

Declaration of interests

LJS reports personal fees from Eisai, outside of the submitted work. TT reports grants from Stockholm County Council, Eisai, Union Chimique Belge (UCB), GlaxoSmithKline (GSK), Bial, and Novartis during the conduct of the study. He also reports personal fees from UCB, Eisai, BMJ India, LivaNova, Sandoz, and Actavis; and grants from Citizens United for Research in Epilespy, outside of the submitted work. MJB reports grants and personal fees from Eisai, UCB Pharma, and Lundbeck, and personal fees from GSK, Bial, GW Pharmaceuticals, Takeda, Sanofi Aventis, and Abbott. CH has nothing to disclose.

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