Update on management of epilepsy in women for the non-neurologist

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ABSTRACT

Epilepsy is a common neurological disorder, prevalent in about 1% of the population. Almost half of the patients with epilepsy are women. Epilepsy and antiepileptic drugs can affect each aspect of the female human life cycle which includes menstrual cycle, contraception, fertility, conception, pregnancy and menopause. The interplay of the female hormonal state and epilepsy is complex and has to be taken in to consideration when managing their epilepsy. This review focuses on the management of women with epilepsy related to their role in reproduction.

INTRODUCTION

Epilepsy is a highly prevalent neurological disorder, affecting nearly 1% of the population.¹ Men and women are affected equally meaning nearly half are women with epilepsy.² About half of the women with epilepsy are in the reproductive age group of 15–49 years.³ This means that there are special problems in the management of women with epilepsy related to their role in reproduction, which start at the menarche and continue until after the menopause. This review focuses on such issues. The possibility of pregnancy should be considered in any woman of childbearing age with epilepsy, as the treatment is often long term. Therefore, management of women with epilepsy needs special consideration. The National Institute for Health and Care Excellence (NICE) has also identified women in the reproductive age group to have specific and unique problems in managing their epilepsy which have been incorporated in this review.

WHAT FACTORS AFFECT CHOICE OF CONTRACEPTION IN WOMEN WITH EPILEPSY?

Carbamazepine, phenytoin, phenobarbital and primidone are older antiepileptic drugs (AEDs) that stimulate (potentiate) the activity of a variety of cytochrome P450 (CYP) enzymes (enzyme-inducing AEDs—table 1). The induction of P450 hepatic cytochrome enzyme activity by these drugs increases the rate of metabolism of both oestrogen and progesterone, thereby lowering the blood concentrations of the combined oral contraceptive pill.⁴ None of the newer AEDs share the broad-spectrum enzyme-inducing activity of older generation agents. However, oxcarbazepine, rufinamide, felbamate, eslicarbazepine acetate and perampanel stimulate the metabolism of the oral contraceptive pill. Topiramate reduces the level of ethinylestradiol by about 30%, but by a different mechanism.⁵ Sodium valproate, the benzodiazepines (clobazam and clonazepam), vigabatrin, lamotrigine, gabapentin, tiagabine, levetiracetam and pregabalin do not

affect liver enzyme activity thus having no effect on the contraceptive pill.²

Thus, women taking enzyme-inducing AEDs should use the combined oral contraceptive pill containing higher doses of oestrogen (at least 50 µg) and tricycle (run three cycles of the active hormonal pill) with a 4-day pill-free interval.⁶ Alternatively, as the failure rate of contraceptive pill with AEDs is about twice that in the general population,⁷ other modalities of contraception may need to be considered.

Enzyme-inducing AEDs can affect the metabolism of the progestogen only pill, progestogen implant and the morning after pill thus requiring higher doses or alternative forms of contraception.² However, the medroxyprogesterone acetate depot injection is unaffected by enzyme-inducing AEDs as its metabolism is proportional to hepatic blood flow which results in an almost 100% first-pass metabolism making the impact of enzyme induction minimal.

In summary, women taking enzyme-inducing AEDs (table 1) should consider alternative methods to hormonal contraception and include the following contraceptive options: medroxyprogesterone acetate depot injection, intrauterine devices and barrier method. Alternatively, if on a hormonal contraceptive method one would need to increase dosage to prevent contraceptive failure.

On the other hand, the combined oral contraceptive pill may reduce the blood concentration of lamotrigine by 40%–60%,⁸ which can result in poor seizure control and needs to be considered especially when introducing the pill to a patient whose seizure control is good. Therefore, alternative contraceptive methods such as medroxyprogesterone acetate depot injection, intrauterine devices and barrier method are options for such a situation.

WHAT IS CATAMENIAL EPILEPSY? HOW DO SEX HORMONES AFFECT EPILEPSY?

Epilepsy is defined as catamenial epilepsy when the periodicity of the exacerbation of the seizure is in association with the menstrual cycle.⁹ Oestradiol has long been known to decrease seizure threshold, and make women more vulnerable to seizures, while progesterone and some of its metabolites decrease the seizure frequency in women, which is related to the antiepileptic effects of progesterone. Thus, catamenial epilepsy can be due to progesterone deprivation and/or a relative increase in oestradiol/progesterone ratio of the serum level.¹⁰ There are three commonly recognised seizure patterns: perimenstrual (day –3 to +3), periovulatory (day 10 to 3) and entire luteal phase in anovulatory cycles (day 10 to 3).¹¹

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Table 1 Enzyme-inducing and non-enzyme-inducing antiepileptic drugs (AEDs)

Enzyme-inducing AEDs	Non-enzyme-inducing AEDs
Carbamazepine	Acetazolamide
Eslicarbazepine acetate	Clobazam
Oxcarbazepine	Clonazepam
Phenobarbital	Ethosuximide
Phenytoin	Gabapentin
Primidone	Lacosamide
Rufinamide	Levetiracetam
Topiramate	Piracetam
Perampanel	Pregabalin
	Sodium valproate
	Stiripentol
	Tiagabine
	Vigabatrin
	Zonisamide

It is sometimes appropriate to treat catamenial epilepsy with intermittent treatment in addition to regular drug treatment. It may then be reasonable to give an additional AED during the days related to the cycle in which seizures are exacerbated once a pattern has been established. A quick acting drug that can be given at full dose such as clobazam is widely used.² There is also evidence to suggest using progesterone as an adjuvant treatment along with AEDs, in controlling the catamenial seizures, is effective compared with placebo, especially for perimenstrually exacerbated subtype.^{10 11}

EPILEPSY AND PREGNANCY

Managing epilepsy during pregnancy is often challenging. The potential malformation risk of AEDs on the fetus at higher doses must be balanced against the maternal and fetal risks associated with uncontrolled seizures on lower doses of AEDs.

WHAT IS THE EFFECT OF EPILEPSY ON PREGNANCY?

In pregnant women, a diagnosis of epilepsy is associated with a small but significant increase in adverse pregnancy outcomes which would require regular monitoring in the antenatal period. In a recent systematic review,¹² and meta-analysis which included 2 837 325 pregnancies found increased odds for the following maternal outcomes: spontaneous miscarriage (OR 1.54, 95% CI 1.02 to 2.32; $I^2=67\%$), antepartum haemorrhage (1.49, 1.01 to 2.20; $I^2=37\%$), postpartum haemorrhage (1.29, 1.13 to 1.49; $I^2=41\%$), hypertensive disorders (1.37, 1.21 to 1.55; $I^2=23\%$), induction of labour (1.67, 1.31 to 2.11; $I^2=64\%$), caesarean section (1.40, 1.23 to 1.58; $I^2=66\%$) and any preterm birth before 37 weeks of gestation (1.16, 1.01 to 1.34; $I^2=64\%$).³ The odds of delivering a baby with fetal growth restriction were also increased in women with epilepsy compared with women without epilepsy (1.26, 1.20 to 1.33; $I^2=1\%$).

The relative impacts of different seizure types are difficult to determine. However, in focal seizures where consciousness is not affected, it is generally accepted that these types of focal seizures have minimal effect on the fetus.¹³ However, in focal seizures where awareness and responsiveness are affected, injuries may occur. Generalised seizures are feared the most. In addition to the possibility of injury, generalised tonic clonic seizures are also known to cause alterations in electrolytes, blood pressure and oxygenation, all of which may harm the fetus. Several animal studies have demonstrated functional alterations of the brain structures due to hypoxia-ischaemia brought on by

generalised seizures.^{14 15} Therefore, generalised seizures compared with focal seizures have a greater impact on the fetus and pregnancy.

It is worth noting that epilepsy is not an indication for early induction of labour or elective caesarean section. Caesarean section is needed in the following instances: if frequent seizures greatly impair cooperation in forthcoming labour and delivery, if a generalised seizure occurs during labour and if there is refractory status epilepticus in the third trimester. These are rare occurrences and most women with epilepsy have normal deliveries.¹⁶

WHAT IS THE EFFECT OF PREGNANCY ON EPILEPSY?

Studies about the frequency and the overall trend of seizures in pregnancy are conflicting: some state there is a reduction (12%), others the opposite (15.8%) and in many cases (70.5%) no changes are observed.¹⁷ Almost all of these apply to AED-treated epilepsy. A recent analysis of the Australian Register of AEDs in Pregnancy suggested that seizure control was less likely to be maintained in AED-untreated pregnancies.¹⁸ Expectedly, there were considerably higher rates of seizure occurrence in women with already active epilepsies at entry into pregnancy. The data suggested that having seizures during pregnancy in those who had ceased AEDs before pregnancy increased the likelihood that AED therapy would be resumed by the end of pregnancy. The study suggested ceasing AEDs that are known teratogens, such as valproate and possibly topiramate, in anticipation of pregnancy may decrease the risk of having a fetal malformation. However, for less teratogenic medication the risk to the fetus of continuing the medication may be positively outweighed by the improvement in seizure control for the mother. This information may help inform women with epilepsy weighing up the risks and benefits of withdrawal of AED therapy in preparation for pregnancy.

WHAT ARE THE TERATOGENIC EFFECTS OF AEDS?

AED teratogenicity should be considered during drug selection for all women of childbearing potential, as many pregnancies are not planned, and most women with epilepsy cannot stop AED treatment due to the danger that seizures present to both mother and fetus.¹⁹ The estimated incidence of total congenital malformations in the general population is 2%–3%, whereas for women undergoing AED treatment it is 6%.²⁰ A range of major congenital malformations such as cleft lip and cleft palate, heart (atrial septal defect, tetralogy of Fallot, ventricular septal defect, aortic coarctation, patent ductus arteriosus and pulmonary stenosis) and urogenital defects can occur in infants born to mothers treated with AEDs.²¹

The European and International Registry of Antiepileptic Drugs in Pregnancy, which includes the Australian Pregnancy Registry, is the largest AED Pregnancy Registry, and has reported dose-related teratogenic effects for all four of the AEDs with the largest sample sizes in its study which includes carbamazepine, lamotrigine, phenobarbital and valproate.²² Overall, the highest malformation rates were seen for valproate (4.7%–10%) and the lowest for lamotrigine (2%–3.4%) (table 2).²³ Valproate doses over 700 mg/day are currently regarded as highly teratogenic, as shown by a number of studies.²⁴ Lamotrigine has been associated with low teratogenic risks, but higher risks of seizures as loss of seizure control can occur in up to 58% of pregnant women.²⁵ One of the major limitations of lamotrigine in pregnancy is the problem of induction by sex hormones thus lowering drug levels in the blood. However, monitoring of blood levels and adjusting the dosage during pregnancy may reduce

Table 2 Fetal malformation risk from pregnancy registries²³

Drug	Malformation risk (%)
Valproic acid	4.7–10
Topiramate	4.2–7.7
Phenobarbital	5.5–7.4
Phenytoin	2.9–6.7
Carbamazepine	2.6–5.6
Lamotrigine	2.0–3.4
Oxcarbazepine	1.8–3.3
Levetiracetam	0–2.4

Registries: International Register of Antiepileptic Drugs and Pregnancy, North American Antiepileptic Drug Pregnancy Register, UK Epilepsy and Pregnancy Register, Medical Birth Register of Norway, Swedish Medical Birth Register.

the seizure risk.²⁶ It has been noted that the combination of low teratogenetic abnormalities and good seizure control during pregnancy makes levetiracetam a better choice for women with childbearing potential. Rates of all seizures in pregnant women taking levetiracetam have been comparable to older AEDs.¹⁹

Several meta-analyses of pregnancy outcomes subsequent to AED polytherapy have revealed that the use of multiple AEDs is associated with higher rates of major malformations ranging from 16.8% to 6.0% versus 3.7% for monotherapy.²⁷ This is especially true for polytherapy regimens which include valproate.²³ Thus, where possible monotherapy is recommended.

In summary, traditional drugs have yielded more evaluable data through pregnancy registries. There is new data to support lower overall rates of malformations with levetiracetam and lamotrigine.²³ The newer AEDs appear less teratogenic than the older ones, but they have been introduced as add-on therapies, and the relevant monotherapy data are less robust.

NICE recommends offering a high-resolution ultrasound scan to pregnant women who are taking AEDs to screen for structural anomalies and this scan should be performed at 18–20 weeks' gestation.²⁸

WHAT ARE THE NON-TERATOGENIC EFFECTS OF CHILDREN EXPOSED TO AEDS IN UTERO?

Evidence from large prospective cohorts indicates that there is a longer term risk to the cognitive and behavioural development of the child exposed in utero to sodium valproate.²⁹ This lends further support to the fact that valproate should not be used in women of childbearing age. Although less certain, there may also be risks associated with phenobarbital and phenytoin exposure. This needs to be considered when counselling prospective mothers who are on these drugs.

HOW CAN PREGNANCY ALTER AED LEVELS IN BLOOD?

Maternal plasma concentrations of AEDs decline as pregnancy progresses and may reduce seizure control.¹⁶ Plasma concentration of AEDs, in particular those metabolised through the CYP system, decreases during pregnancy. Phenytoin and phenobarbital are examples for such increases in metabolism.²⁹ Plasma concentration of AEDs metabolised through glucuronidation such as lamotrigine and oxcarbazepine can markedly decrease over the course of the pregnancy. Lamotrigine plasma concentrations can decline during gestation to as much as 30% or less of prepregnancy values.³⁰ Lower concentration of albumin that occurs during pregnancy leads to a reduction in the percentage of drug molecules bound to proteins. In response to a decrease of the total concentration, there is therefore a reduction of the

pharmacologically active percentage of the drug (the unbound fraction).^{31–32} This can affect drugs with high protein binding, especially phenytoin and valproic acid. Reduction of gastric motility,³³ increase of plasma volume³⁴ and increase of renal blood flow³⁵ are other mechanisms in which serum concentrations of AEDs can be altered during pregnancy.

It has been found that when AEDs in the blood fell >35% from preconception baseline, seizures worsened significantly during the second trimester.³⁶ This has been especially demonstrated for both lamotrigine and levetiracetam. It has been suggested to monitor AED serum concentrations with dose adjustment in pregnant women with epilepsy. However, not all centres will have facilities to monitor drug levels in the blood of the full spectrum of AEDs and there is no clear consensus with regard to drug monitoring as some of the data are conflicting. For example, some data suggest that levetiracetam does not lead to a clinically less good seizure outcome during pregnancy.³⁷ Most centres however increase the dose of lamotrigine during the second and third trimesters to counter worsening seizure control due to decreasing plasma levels.

WHAT IS THE ROLE OF FOLIC ACID IN TREATING PREGNANT WOMEN WITH EPILEPSY?

It is suggested that folic acid supplements reduce the risk of neural tube defects in the offspring of women at risk.³⁸ Valproate and carbamazepine are known to be associated with an increased risk of neural tube defects, estimated at 1.5% and 0.5%, respectively.³⁹ Most guidelines advocate that all women taking AEDs contemplating pregnancy should be given a folic acid supplement to prevent teratogenicity though robust evidence for this is lacking.⁴⁰ Folic acid 5 mg once daily is the widely recommended dosage.⁴¹

WHAT IS THE PLACE OF VITAMIN K IN PREGNANCY?

The theoretical risk of bleeding due to degradation of fetal vitamin K and inhibition of γ -carboxy-glutamic acid for the precursors of coagulation factors II, VII, IX and X by enzyme-inducing AEDs is sufficient for all pregnant women taking these drugs to take oral phytomenadione (vitamin K₁) 20 mg daily for at least 1 month before delivery to reduce the risk of bleeding in the first 24 hours, and vitamin K₁ 0.5 mg should be given intramuscularly immediately after delivery.² However, Kaaja *et al*⁴² found no increase in the incidence of bleeding in 662 infants of mothers taking enzyme-inducing AEDs, compared with 1324 controls, the numbers may have been insufficient to show an effect.

SHOULD WOMEN WITH EPILEPSY BREAST FEED?

Breast feeding for most women and girls taking AEDs is generally safe.²⁸ Thus, all women and girls with epilepsy should have no concerns regarding breast feeding and be encouraged to breast feed.

HOW DOES MENOPAUSE AFFECT EPILEPSY?

The hormonal changes in menopausal transition seem to have an effect on seizure susceptibility in certain women. Women with catamenial epilepsy may experience an increase in seizure frequency during the perimenopause and a decrease after menopause.^{43–44} This is due to high oestrogen levels in perimenopause, and low oestrogen levels in postmenopause.

There is some conflicting evidence with regard to seizure frequency and severity in women during menopause. A study suggested that similar number of women had no change, increase or decrease in their seizure frequency after menopause.⁴⁴ It has

also been shown that the frequency and severity of the seizures in premenopausal women were similar with those in perimenopausal and menopausal women.⁴⁵

DOES HORMONE REPLACEMENT THERAPY AFFECT SEIZURE CONTROL?

Standard hormone replacement therapy (HRT), which includes oestrogen and a progestin, in postmenopausal women with epilepsy can have an effect on seizures that is more evident than that of oral contraceptives in premenopausal women with epilepsy, because reproductive hormone levels during menopause are low and do not vary.⁴⁶ Combined oestrogen plus progesterone HRT in postmenopausal women with epilepsy has been associated with an increase in seizure frequency.⁴⁷ Thus, it would be prudent to closely monitor women who start hormone therapy as their AED needs may change. Enzyme-inducing AEDs can also affect the metabolism of HRT which may cause problems with efficacy similar to effects on contraception as discussed previously.

AED use is an independent predictor of increased risk of osteoporosis and subsequent fractures in menopausal women.⁴⁸ This increased risk is due to the effect of enzyme-inducing AEDs on vitamin D, added to the natural risk of osteoporosis because of age and postmenopausal status.⁴⁹ Therefore, it is recommended that vitamin D supplementation should be considered for at-risk patients taking long-term enzyme-inducing AEDs.⁵⁰

PRACTICE POINTS

Box 1 Recommendations for contraception

- ▶ Alternative forms of contraception or higher doses have to be considered in patients using hormonal contraception and enzyme-inducing antiepileptic drugs (AEDs) to prevent contraceptive failure (NICE). Medroxyprogesterone acetate depot injection is a hormonal contraceptive option unaffected by enzyme-inducing AEDs and is an option for women on enzyme-inducing AEDs.
- ▶ Review lamotrigine dosage as combined oral contraceptive pill may reduce the blood concentration of lamotrigine potentially leading to breakthrough seizures (NICE).

*NICE in parenthesis represents guidelines recommended by NICE. NICE, National Institute for Health and Care Excellence.

Box 2 Recommendation during preconception

- ▶ Counsel regarding the need for good seizure control with antiepileptic drugs (AEDs) during pregnancy for women planning conception.
- ▶ Valproate is not recommended for women of childbearing age with focal epilepsies. For generalised epilepsy, lamotrigine and levetiracetam are preferred AEDs unless advised differently by an epilepsy specialist for exceptional circumstances.
- ▶ Lamotrigine is a recommended AED during pregnancy as it is associated with low teratogenic risks. However, this may have higher risks of seizures in pregnancy due to lower plasma levels which may require dose adjustment for optimal control (NICE).

- ▶ Combination of low teratogenicity and good seizure control during pregnancy makes levetiracetam an alternative in place of lamotrigine.
- ▶ Multiple AEDs is preferred less as this is associated with higher rates of major congenital malformations; thus, monotherapy at the lowest effective dose where possible is recommended (NICE).
- ▶ Folic acid 5 mg should be given to all women taking AEDs contemplating pregnancy to prevent teratogenicity (NICE).

*NICE in parenthesis represents guidelines recommended by NICE. NICE, National Institute for Health and Care Excellence.

Box 3 Recommendations during pregnancy

- ▶ Closer monitoring of pregnancy for women with epilepsy is recommended (with or without antiepileptic drug (AED) treatment) as they have a risk for spontaneous miscarriage, antepartum haemorrhage, postpartum haemorrhage, hypertensive disorders, induction of labour, caesarean section, preterm birth before 37 weeks of gestation and fetal growth restriction.
- ▶ Perform high-resolution ultrasound scan to screen for structural anomalies at 18–20 weeks' gestation in pregnant women who are taking AEDs (NICE).
- ▶ AEDs could be reinstated (if discontinued prior to conception) or increased after 12 weeks of pregnancy to gain good seizure control as teratogenic effects of AEDs ends at this time.
- ▶ Lamotrigine, oxcarbazepine and levetiracetam dosage may have to be increased as maternal plasma concentrations can markedly decline as pregnancy progresses affecting seizure control.
- ▶ Pregnant women taking enzyme-inducing AEDs should take oral vitamin K 20 mg daily for at least 1 month before delivery to reduce the risk of neonatal bleeding in the first 24 hours, and vitamin K (0.5 mg) should be given intramuscularly to the neonate immediately after delivery (NICE).
- ▶ Aim to achieve maximum control of generalised seizures as generalised seizures compared with focal seizures have a greater impact on the fetus and pregnancy (NICE).
- ▶ Caesarean section is indicated if frequent seizures impair cooperation in forthcoming labour or in the case of refractory status epilepticus in the third trimester.

*NICE in parenthesis represents guidelines recommended by NICE. NICE, National Institute for Health and Care Excellence.

Current research questions

- ▶ What are the risks versus benefits of omitting antiepileptic drugs in women planning to conceive?
- ▶ How can the choice of contraception affect women with epilepsy?
- ▶ What impact do female sex hormones have on epilepsy at various stages of a woman's life?

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Main messages

- ▶ Enzyme inducing AEDs interact with hormonal forms of contraception which can result in contraceptive failure.
- ▶ The potential malformation risk of AEDs on the foetus at higher doses must be balanced against the maternal and foetal risks associated with uncontrolled seizures on lower doses of AEDs.
- ▶ The highest teratogenicity from all AEDs is seen with valproate. This risk increases with higher doses and polytherapy with valproate.
- ▶ The lowest foetal malformation risk is seen with levetiracetam.
- ▶ Enzyme inducing AED use is an independent predictor of increased risk of osteoporosis and subsequent fractures in menopausal women. Vitamin D is metabolized by these AEDs prompting the need for supplementation.

Self assessment questions

Please answer true or false for the below statements.

1. Levetiracetam as an antiepileptic drug is a good choice for women with childbearing potential.
2. Combined oestrogen plus progesterone hormone replacement therapy in postmenopausal women with epilepsy has been associated with a decrease in seizure frequency.
3. There is a long-term risk to the cognitive and behavioural development of a child exposed in utero to sodium valproate.
4. Catamenial epilepsy can be due to oestrogen deprivation and/or a relative increase in progesterone/oestradiol ratio of the serum level.
5. Breastfeeding is unsafe in patients on antiepileptic drugs.

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Answers

1. True
2. False
3. True
4. False
5. False