Epilepsy and pregnancy: identifying risks

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ABSTRACT

Pregnancy is a time of physical, physiological and psychological challenge. For women with epilepsy, as well as its potential for joy and fulfilment, pregnancy may bring additional risks and difficulties. Clinicians must anticipate and prevent these complications, ensuring that pregnancy, delivery and motherhood proceed without obstetric or medical complications, using available evidence to balance individual risks of undertreatment and overtreatment. Here we review epilepsy management in pregnancy, identifying some of the known effects of epilepsy and its treatment on gestation, fetal malformation, delivery, and neurocognitive and behavioural development. We outline strategies to reduce obstetric and fetal complications in women with epilepsy, while recognising the sometimes competing need to maintain or improve seizure control. We reinforce the importance of identifying those at highest risk, who may require additional measures or safeguards.

INTRODUCTION

Epilepsy has a prevalence of 0.5%–1.0% and affects 50 million people globally,1 2 of whom 1.5 million are women of reproductive age.2 While most women with epilepsy will have uncomplicated pregnancies and healthy children, there is evidence for an increased risk of complications, including increased maternal mortality and adverse outcomes in their babies.

This review aims to summarise the current evidence and to provide practical advice to optimise maternal health, while minimising the risks to fetal development.

Excellent communication between neurology and obstetric teams is key, facilitating easy access to all aspects of care, as recommended by UK-wide audits carried out by the multiprofessional organisation MBRRACE-UK.3 Advice should be individualised and influenced by having identified and stratified the risks for each pregnancy. Clinicians should consider maternal attitudes to the risks of seizures and antiseizure medications to inform management before, during and after pregnancy.

Maternal health in women with epilepsy

Maternal mortality

The risk of maternal mortality in women with epilepsy is probably 5–10 times higher than background.4 5 The MBRRACE-UK report3 showed a similar increase in mortality. During 2016–2018 in the UK and Ireland, 22 women died from causes related to epilepsy during or up to a year after the end of pregnancy. Of these, 18 died from sudden unexplained death in pregnancy (SUDEP), two from status epilepticus and two from drowning. This rate of SUDEP is more than double that found in 2013–2015. Of the 19 patients with available records, very few had received pre-pregnancy counselling; epilepsy was controlled before pregnancy in only three and fewer than one-third had an epilepsy specialist review during pregnancy. Four were taking no antiseizure medication during pregnancy, despite three of these having ongoing seizures, and six were prescribed lamotrigine monotherapy at the time of death. With a case–control study from Norway finding that lamotrigine was associated with an increased risk of SUDEP,6 the impact of altered serum lamotrigine concentrations in pregnancy on seizure control has become a significant issue.

Obstetric morbidity

Several studies have highlighted the obstetric risks associated with epilepsy4 (table 1), including pregnancy-induced hypertension, pre-eclampsia, antepartum and postpartum haemorrhage, induction of labour and instrumental deliveries.
Table 1  Adjusted OR of maternal complications in patients with epilepsy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal death</td>
<td>11.46</td>
<td>8.64 to 15.19</td>
</tr>
<tr>
<td>Induction of labour</td>
<td>1.14</td>
<td>1.12 to 1.16</td>
</tr>
<tr>
<td>Pregnancy-related hypertension</td>
<td>1.30</td>
<td>1.27 to 1.33</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>1.59</td>
<td>1.54 to 1.63</td>
</tr>
<tr>
<td>Seizures with pre-eclampsia</td>
<td>5.18</td>
<td>4.65 to 5.77</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>1.38</td>
<td>1.31 to 1.45</td>
</tr>
<tr>
<td>Severe postpartum haemorrhage</td>
<td>1.76</td>
<td>1.61 to 1.93</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>1.11</td>
<td>1.07 to 1.15</td>
</tr>
<tr>
<td>Preterm labour</td>
<td>1.54</td>
<td>1.50 to 1.57</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>1.17</td>
<td>1.11 to 1.23</td>
</tr>
<tr>
<td>Poor fetal growth</td>
<td>1.68</td>
<td>1.61 to 1.750</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>1.04</td>
<td>1.02 to 1.06</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1.27</td>
<td>1.17 to 1.38</td>
</tr>
</tbody>
</table>

Maternal seizures
Seizures in pregnancy pose risks to both mother and baby. Maternal status epilepticus was associated with adverse outcomes in 4 of 21 cases in a Europe-wide collaborative observational study, EURAP, including one perinatal death and three major congenital malformations.

Epilepsy control in pregnancy
In a review of 3806 pregnancies, 33% of patients recorded seizures, with 15% experiencing convulsive seizures. In those with refractory epilepsy, around 40% had convulsive seizures during pregnancy, compared with less than 20% in those seizure free for a year before conception. After 6 years of seizure freedom, the risk of a pregnancy-related bilateral convulsive seizure was below 10%. Patients taking with a higher drug load were more likely to have seizures in the first trimester (35%) than those taking monotherapy (15.3%). Seizure freedom during pregnancy varied with antiseizure medication exposure, with lower rates of seizure freedom for those taking lamotrigine (58.2%) compared with valproate (75%), carbamazepine (67.35%) or phenobarbital (73.4%). The lamotrigine cohort had significantly more convulsive seizures (21.1%) than those taking valproate (11.5%), carbamazepine (12.6%) or phenobarbital (14.0%) cohorts.

Table 2 lists those factors likely to predict convulsive seizures in pregnancy.

In contrast, one case–control study that included a few patients taking lamotrigine found no clear change in seizure frequency during pregnancy. A further case–control study of 351 pregnant women (109 non-pregnant controls) also found that when women with epilepsy are managed very carefully during pregnancy, including with monitoring of antiseizure medication serum concentrations and dose adjustments to maintain these, there was no change in seizure control, compared with non-pregnant women.

Table 2  Seizure occurrence rates in patients with epilepsy during pregnancy

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing seizures</td>
<td>78.4% vs 22.3% (3.51 (3.13 to 3.94))</td>
</tr>
<tr>
<td>Antiseizure medication</td>
<td>62.6% vs 37.5% (1.67 (1.51 to 1.85))</td>
</tr>
<tr>
<td>Generalised versus focal epilepsy</td>
<td>37.1% vs 48% (0.64 (0.53 to 0.71))</td>
</tr>
</tbody>
</table>

Reasons for potential seizure deterioration in pregnancy
Adherence changes
Awareness of the potential for harm resulting from prenatal exposure to antiseizure medications may lead to reduced adherence and account for some loss of efficacy in pregnancy. Around 40% of women with epilepsy have low adherence to antiseizure medications during pregnancy, which is worse than for treatments prescribed to pregnant women with other chronic conditions. The extent of this pregnancy-related drop in adherence is variable and unpredictable. Data from a Scottish national prescribing data set showed that 32/71 (45.1%) of women with epilepsy had poor adherence to at least one of their antiseizure medications before booking, compared with 30/71 (42.3%) following booking.

A study of hair drug concentrations suggested that around 15% of women stopped or reduced their antiseizure medications during pregnancy without prior consultation; pregnancy-related pharmacokinetic changes might also have contributed to the findings.

Pharmacokinetics in pregnancy
Pregnancy induces significant physiological and metabolic changes. Knowledge about pharmacokinetic changes during each trimester is improving (see ref 13 for an excellent review). Tables 3 and 4 summarise the effects of pregnancy on antiseizure medications. A full discussion of the nature of these changes is beyond the scope of this review, but in summary.

Absorption
This can be reduced by changes in intestinal motility or sustained vomiting.

Distribution
Changes in volume of distribution and protein binding could in theory reduce antiseizure medication concentrations and in some cases necessitate measurement of free serum concentrations.
Metabolism
Antiseizure medication metabolism may increase, particularly of those metabolised through glucuronidation (e.g., lamotrigine, oxcarbazepine and valproate), although the extent of this change during pregnancy varies considerably between individuals and is difficult to predict.13 16–18

Excretion
Increases in renal blood flow and glomerular filtration rate are most prominent in the first two trimesters.19 This can lead to reduced concentrations of those antiseizure medications that are mainly excreted renally (e.g., gabapentin, levetiracetam and pregabalin) and may partly explain the pronounced increase in clearance of lamotrigine and its N2-glucuronide metabolite.20 21

Studies of pregnancy-related pharmacokinetics
There have been several studies of lamotrigine serum concentrations during pregnancy (table 4). While modes of measurement vary widely, all the evidence is consistent with a trend to falling serum concentrations as pregnancy progresses, even allowing for the tendency for clinicians to increase daily dose during pregnancy.

The wider effects of pregnancy on antiseizure medication pharmacokinetics have been excellently reviewed elsewhere.22 While phenytoin serum concentrations drop markedly, there is less effect on free (unbound) concentrations. While there may be modest reductions in serum concentration of carbamazepine and valproate, free concentrations do not fall. Some women show decreased concentrations of levetiracetam, oxcarbazepine, phenobarbital, topiramate and zonisamide. A prospective study found a twofold increase in the clearance in levetiracetam during the first trimester and for topiramate and oxcarbazepine by the second trimester.23

Fetal health in babies of women with epilepsy
Effect of seizures on fetal health
The long-term effect of seizures on fetal health is difficult to separate from the effects of antiseizure medications, but case reports imply physiological changes in the fetus following focal and generalised seizures.24 Convulsive seizures are of most concern, with preclinical studies demonstrating neurological and psychological sequelae in babies exposed to convulsive seizures in utero.24

Seizures during pregnancy have been associated with an increased incidence of preterm birth and babies with low birth weight or who are small for gestational age, even in those without antiseizure medication exposure.25 One study showed that having more than five bilateral convulsive seizures during pregnancy was an independent risk factor for cognitive delay.26

Table 3  Effect of pregnancy on individual antiseizure medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Elimination</th>
<th>Decrease in serum concentration during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Hepatic</td>
<td>0%–42%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Renal — unchanged</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Hepatic glucuronidation</td>
<td>See table 4</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Renal &gt; hydrolysis</td>
<td>40%–60%</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Hepatic glucuronidation of active metabolite</td>
<td>28%–36%</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Hepatic</td>
<td>50%–55%</td>
</tr>
<tr>
<td>Primidone</td>
<td>Derived fromphenobarbital</td>
<td>70%</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Mainly renal unchanged</td>
<td>13%–40%</td>
</tr>
<tr>
<td>Valproate</td>
<td>Hepatic glucuronidation</td>
<td>0%–28%</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Mainly hepatic, 15%–30% renal unchanged</td>
<td>40%–50%</td>
</tr>
</tbody>
</table>

Table 4  Lamotrigine changes in pregnancy and postpartum period

<table>
<thead>
<tr>
<th>Author</th>
<th>Comparative measure</th>
<th>Preconception</th>
<th>Trimester 1</th>
<th>Trimester 2</th>
<th>Trimester 3</th>
<th>Post partum (time of sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennell et al66</td>
<td>Increase in clearance of preconception</td>
<td>91% (±107%)</td>
<td>149% (±142%)</td>
<td>261% (±194%)</td>
<td>50%±69%</td>
<td>50%±69%</td>
</tr>
<tr>
<td>Fotopoulou et al67</td>
<td>Median ratio lamotrigine dose:serum (1st and 3rd quartiles)</td>
<td>39 (39–41)</td>
<td>77 (68–154)</td>
<td>92 (76–167)</td>
<td>97 (74–110)</td>
<td>35 (35–36) (at 3 weeks)</td>
</tr>
<tr>
<td>Petrenaite et al68</td>
<td>Mean ratio serum lamotrigine: dose</td>
<td>63.5±30.8</td>
<td>46.7±18.3</td>
<td>22.1±5.4</td>
<td>21.7±7.1</td>
<td>70±10 (at 6 weeks)</td>
</tr>
<tr>
<td>de Haan et al69</td>
<td>Mean ratio serum lamotrigine concentration to dose (as percentage of preconception baseline)</td>
<td>82%±14%</td>
<td>51%±14%</td>
<td>97%±15%</td>
<td>48%±10%</td>
<td></td>
</tr>
<tr>
<td>Öhman et al70</td>
<td>Mean ratio lamotrigine dose:plasma</td>
<td>227±74</td>
<td>66.5±17.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effect of antiseizure medications on fetal health

*Intrauterine growth*

Antiseizure medications taken during pregnancy have been associated with babies who are small for gestational age and with reduced head circumferences. In one study, 11% of infants born to women with epilepsy who took these in pregnancy were small for gestational age, compared with 5% for those born to women with epilepsy, who were not taking these medications. The risks differ between antiseizure medications, with current evidence implicating topiramate and to a lesser extent carbamazepine, valproate and those on polytherapy combinations.

Major congenital malformations

Major congenital malformations are increased by a factor of 2–3 (to 4%–9%) in children exposed to antiseizure medications during pregnancy. The risk is higher in pregnancies exposed to polytherapy and increases with more medications taken. The risk is highest for valproate. Prior pregnancy outcome is important when determining individual malformation risk; women with past pregnancies with major congenital malformations are at higher risk of this in future babies. Fetal health must be balanced against the risk of seizures and complications of seizures, including SUDEP.

*Sodium valproate*

The risk of a major congenital malformation is approximately 10% for pregnancies exposed to sodium valproate. This risk is dose dependent with a reported risk of 5.6% in pregnancies exposed to less than 700 mg daily dose of valproate, 10.4% in pregnancies exposed to 700–1500 mg/day and 24.2% in those exposed to over 1500 mg/day. Malformations reported include neural tube defects, cardiac defects, clefting abnormalities, genitourinary defects and hypospadias.

*Carbamazepine*

The risk of a major congenital malformation for carbamazepine is reported to be 4%–5%. While the UK and Ireland Epilepsy and Pregnancy Register reported a rate just above background, EURAP reported a doubling of the rate, the difference likely reflecting differences between the follow-up times for each of the pregnancy registries. There is a dose-dependent relationship, with a 3.4% major congenital malformation rate in those exposed to less than 400 mg/day, compared with 8.7% in those exposed to over 1000 mg/day. Malformations reported included cardiac defects, clefting abnormalities, neural tube defects, skeletal malformations, genitourinary defects and hypospadias.

*Lamotrigine, levetiracetam and newer antiseizure medications*

For the newer medications, the most information is available for lamotrigine and levetiracetam, with major congenital malformation rates similar to background. Tomson et al did show a dose-related increase in malformation rate with lamotrigine above 325 mg/day. Available information for oxcarbazepine does not suggest an increased risk of major malformations. There is less information for the other new medications, although there have been concerns raised for topiramate, in particular for clefting abnormalities. There are very few data on safety of other medications, including zonisamide, lacosamide, perampanel and eslicarbazepine acetate. This highlights the need for careful ongoing monitoring through reporting to pregnancy databases.

*Phenobarbital and phenytoin*

Phenytoin and phenobarbital have increased rates of major congenital malformation rates, which are lower than for valproate but still higher than the background rate.

Antiseizure medication polytherapy

It is difficult to interpret polytherapy results due to the number of potential combinations. In general, there is an increased risk of major congenital malformations, although regimens containing valproate appear to confer the greatest risk. Results from the North American Pregnancy Register showed a major congenital malformation risk of 9.1% among infants exposed to lamotrigine taken along with valproate as part of a polytherapy regimen, compared with 2.9% for lamotrigine plus any other antiseizure medication (1.5; 0.7–3.0). This was also the case for carbamazepine, with risks of 15.4% when carbamazepine was taken with valproate as part of a polytherapy regimen, compared with 2.5% for carbamazepine plus any other antiseizure medication. It has been suggested that low-dose valproate as part of a polytherapy regimen might be safer with respect to major congenital malformation than for high-dose valproate taken as monotherapy. Valproate taken as part of polytherapy regimens in total daily doses of less than 700 mg/day was associated with a malformation rate of 5.4%, compared with 11.0% for monotherapy doses above 700–1500 mg/day and 24.0% for doses greater than 1500 mg/day.

Cognitive and other neurodevelopmental effects

Studies have consistently shown lower cognitive functioning in children of women with epilepsy. While the risks vary between antiseizure medications, they are highest for valproate. Overall, 30%–40% of children exposed to valproate during pregnancy experience neurodevelopmental disorders. In contrast, available information for carbamazepine, lamotrigine and levetiracetam is more reassuring, although more data are required.

The Neurodevelopmental Effects of Antiepileptic Drugs study assessed IQ and multiple other
cognitive domains in 224 subjects at 6 years of age. Mean IQ in the valproate group was reduced by 11 points compared with the lamotrigine and phenytoin groups, and by 8 points compared with the carbamazepine group. The association between valproate use and IQ was dose dependent with mean IQs of 104 for doses below 1000 mg/day, but 94 for doses above 1000 mg/day. Valproate doses over 1000 mg/day were associated also with significantly reduced measures of verbal and non-verbal ability, memory and executive functioning. A Cochrane review reported similar results, including 22 prospective cohort studies and six registry-based studies. A significant correlation between neurodevelopmental disorders and facial dysmorphism has been reported for valproate.

Information on other newer antiseizure medications is restricted to levetiracetam and topiramate. Due to the size of the cohorts studied and the timing of assessments, the results need to be viewed with caution. In a study comparing cognitive development in children up to 3 years of age, those exposed to levetiracetam in utero were not at an increased risk of delayed early development compared with control children. In contrast, those exposed to valproate scored significantly lower. For topiramate, there have been mixed results. While one study on 27 topiramate-exposed children found no changes in IQ, memory, language and attention, further research is clearly required.

Table 5: Identification and management of higher risk pregnancies

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk associated</th>
<th>Mitigation required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconceptual refractory epilepsy</td>
<td>Increased risk of breakthrough seizures in pregnancy</td>
<td>► Rationalise treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Review adherence.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Consider serum concentration monitoring (see table 6).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Consider additional antiseizure medication.</td>
</tr>
<tr>
<td>Antiseizure medication polypharmacy</td>
<td>Increased risk of major congenital malformation and neurocognitive problems</td>
<td>Review medication and minimise exposure.</td>
</tr>
<tr>
<td>Valproate treatment</td>
<td>Increased rate of major congenital malformation and neurocognitive problems</td>
<td>► Withdraw or minimise dose (if possible)—may require EEG monitoring?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Change to sustained release preparation?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Spread dose across the day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Reinforce coprescription of folate.</td>
</tr>
<tr>
<td>Levetiracetam or lamotrigine monotherapy</td>
<td>Worsening seizure control as pregnancy progresses</td>
<td>Monitor serum concentrations.</td>
</tr>
<tr>
<td>Underlying condition that may worsen in pregnancy (eg, meningioma)</td>
<td>Worsening seizures</td>
<td>Consider more frequent assessments.</td>
</tr>
</tbody>
</table>

Factors affecting management of pregnancy in women with epilepsy

There are three key phases of intervention: preconceptual phase, during pregnancy (at least once each trimester) and immediately post partum. Services should allow provision of epilepsy care throughout these. The management of each phase is affected by four key issues.

Stratification and reduction of risk in patients with epilepsy

The months (or years) before pregnancy are the ideal time for clinicians to help to minimise the risk of harm to the mother and baby from seizures or exposure to antiseizure medications. Repeated discussions should assess risk factors to fetal and maternal health from epilepsy and antiseizure medications (see table 5). Individualised counselling will allow the woman to make an informed choice on treatment and management plans in advance of conception.

Valproate use in women of reproductive age

The congenital malformation and cognitive risks of valproate use have prompted regulatory changes in many countries. These require provision of up-to-date information and a formal recurrent consent procedure to be completed. In the UK, in addition to an annual specialist review, women taking valproate must be offered highly effective contraceptive methods, including copper intrauterine device, levonorgestrel

Table 6 Therapeutic drug monitoring during pregnancy—advantages and disadvantages

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipates falling concentrations and increases treatment pre-emptively.</td>
<td>Increases drug load even in patients with well-controlled epilepsy.</td>
</tr>
<tr>
<td>Better seizure control.</td>
<td>Increases cost and inconvenience of pregnancy care.</td>
</tr>
<tr>
<td>Reduced risks of maternal harm.</td>
<td>Maintains relatively higher degree of fetal exposure to antiseizure medications.</td>
</tr>
<tr>
<td>Reduced risks to fetus from seizures.</td>
<td>Unpredictability of pregnancy-related pharmacokinetic change means monitoring may not pick up changes in level.</td>
</tr>
<tr>
<td></td>
<td>Delay in receiving results of testing (up to 6 weeks in some situations) means monitoring may not pick up changes in serum concentration.</td>
</tr>
</tbody>
</table>

13.5 mg/ 19.5 mg/ 52 mg intrauterine system, progesterone-only implant or sterilisation.

Some patients rely on valproate as an effective treatment of their epilepsy and may opt to continue it, despite the advice. How to deal with this and other situations, including those who fail to engage with the programme, those with intellectual disabilities and patients in emergency situations, has been the subject of a recent multidisciplinary review.47

The risks from sodium valproate are sufficiently high that we lay out separately below our suggested measures for dealing with this at each stage of the reproductive process.

Risks and benefits of therapeutic drug monitoring

While there is no class A evidence of benefits of therapeutic drug monitoring during pregnancy, converging evidence from several studies led to an International League Against Epilepsy Task Force report on monitoring serum concentrations of lamotrigine, oxcarbazepine, gabapentin, topiramate, levetiracetam and zonisamide. The UK Medicines and Healthcare products Regulatory Agency (MHRA)35 36 similarly recommends routinely monitoring concentrations of lamotrigine before, during and after pregnancy. For oxcarbazepine, levetiracetam and phenytoin, it suggests clinical monitoring, with serum concentrations checked where the clinician feels this is necessary.

Monitoring antiseizure medication drug concentrations during pregnancy is not without its difficulties. Even if performed regularly, routine checking may ‘miss’ rapid drops in concentrations of some antiseizure medications, especially since pregnancy-related changes display marked interindividual and intraindividual variations. The delay in availability of results for some of the more recently available antiseizure medications may render ‘real time’ monitoring of these more difficult (table 6).

There has been one randomised study looking at the effect of monitoring during pregnancy.49 This study involved 261 pregnant women with epilepsy, who had demonstrated ≥25% drop in serum concentrations of antiseizure medications, randomising to either routine care (with consideration of reactive dose changes) or to clinical monitoring (ie, reoccurrence of breakthrough seizure); there was no difference in seizure control between the two groups. There was an increase in umbilical cord concentration of antiseizure medications in those randomised to active management of serum concentrations, although this was not associated with more adverse outcomes in babies. The study’s sensitivity might have been hampered by several factors, including the period under study, grouping together of all antiseizure medications and the lack of a standardised approach to up titration of medication doses after a drop in serum concentrations.

In considering the recommendations, monitoring plans should be agreed with each woman, preferably in advance of conception. The decision should take into account available information on risk of fetal harm from antiseizure medications, and the risk of harm and social disruption (eg, driving) arising from seizures.

Where pre-pregnancy serum concentrations are available, the recommendation is to adjust antiseizure medication dose to maintain the individual’s target concentration, avoiding reductions of more than 35% from the baseline non-pregnant target concentration.39 Four-weekly measurement has been recommended, with additional checks being undertaken if clinically indicated, for example, due to changes in seizure control, medication side effects or concerns about medication adherence.

If antiseizure medication monitoring is not available, then an increase in dose might be considered at the end of the first trimester for those medications known to undergo marked changes during pregnancy (lamotrigine, levetiracetam and oxcarbazepine), especially where there is a history of pre-pregnancy breakthrough bilateral convulsive seizures. There is no evidence to provide detailed guidance in this situation and we would recommend discussion with the patient to outline the benefits and drawbacks of dose changes. If breakthrough seizures occur, dose increases should be considered, especially for bilateral convulsive seizures, sleep-related seizures and where the antiseizure medication is prone to pregnancy-related decreases. Exacerbation of other seizure types (eg, focal aware seizures, focal impaired awareness seizures or myoclonic seizures) may also prompt counselling on possible need for dosage increases.

While some might argue that there is a potential for harm arising from higher fetal exposure to antiseizure medications, it is worth noting that the intention of monitoring is to maintain a stable serum concentration,
only increasing if clinically indicated and after full discussion with the patient. The utility of monitoring is obviously enhanced if there are pre-pregnancy antiseizure medication serum concentrations, with which to compare.

High-dose folate supplementation
Adequate folate should be prescribed preconceptually until at least the end of the first trimester. The optimum dose of folate and its effect on incidence of major congenital malformations in humans is unclear.\textsuperscript{53, 51} Periconceptual folate intake has been associated with higher child IQ at age 6 for all antiseizure medications studied.\textsuperscript{52}

Studies in the general population have shown reduced risk of severe language delay with folate supplementation in early pregnancy, and improved measures of verbal communication with supplemental preconceptual folate.\textsuperscript{53, 54} Some guidelines advocate prescribing folate 5 mg daily for at least 3 months before pregnancy and throughout pregnancy.\textsuperscript{55}

Management of each stage of pregnancy in women with epilepsy
The current optimal management of all women before, during and after pregnancy is outlined in several guidelines and papers.\textsuperscript{5, 46, 53–57} The important aspects of care in pregnancy are the same as those for all patients with epilepsy; that is, minimising hazardous seizures (especially prolonged convulsive and sleep-related seizures), while ensuring exposure to the fewest antiseizure medications at the lowest possible doses.

Preconceptual management
Preconceptual counselling should be available to all women with epilepsy, starting at the time of diagnosis, and repeated regularly. In one study, only half of patients recalled information related to epilepsy and pregnancy.\textsuperscript{58}

The importance of medication adherence and provision of higher dose folate supplementation should be covered. Standard general health advice such as weight management, smoking cessation and maintaining healthy levels of exercise should be covered at some point during nursing or medical review.

Discussion around maintenance of a good sleep pattern during pregnancy may help reduce seizure frequency. A baseline measurement of antiseizure medication serum concentration, particularly for those medications that demonstrate falling serum concentrations in pregnancy, should be offered as per ILAE and MHRA guidelines.

Managing valproate use preconceptually
All women receiving valproate in the UK should have an annual assessment resulting in completion of the Annual Risk Acknowledgement Form.\textsuperscript{59} Consideration should be given as early as possible to reducing or withdrawing valproate, mindful that some women may respond only to this. Where possible, valproate should be changed to another antiseizure medication, but fetal risks may be increased if this worsens seizure control or results in polytherapy.

EEG monitoring may allow consideration of risk of reducing or withdrawing valproate in patients with well-controlled generalised epilepsies: bilateral discharges on awakening in an asymptomatic patient may warn of increased risk of breakthrough seizures with dose reduction.

Management during pregnancy
We recommend specialist epilepsy review during each trimester for all women with epilepsy, working with obstetric services. Management requires a balance between the competing demands of minimising seizure recurrence, reducing seizure complications and minimising exposure to antiseizure medications. Monitoring of antiseizure medication serum concentrations should be offered in line with recommendations detailed above. Detection of antiseizure medication-related fetal abnormality is best done with high-resolution ultrasound scanning by at least 20 weeks’ gestation.\textsuperscript{55}

Minimise seizure occurrence during pregnancy
The concerns are similar to those outlined in preconceptual management. Concerns about maternal safety mandate more active management in those patients experiencing convulsive seizures, prolonged seizures or sleep-related seizures. The increased risk of seizure worsening in those taking lamotrigine should prompt discussion about proactive dose increases and therapeutic drug monitoring as recommended by the ILAE and MHRA. It is important to identify those patients at higher risk of breakthrough generalised seizures: those with previous breakthrough seizures on medication reduction, or those with idiopathic (genetic) generalised epilepsy with generalised epileptiform discharges on EEG.

Managing antiseizure medication-associated risks during pregnancy
Pregnancies in women with epilepsy should be supervised in obstetric units with access to high-resolution ultrasound scanning and full access to all available prenatal tests. UK guidelines\textsuperscript{55, 56} advocate high-resolution scanning at 18–20 weeks’ gestation. Timely access to physicians, neurologists and epilepsy nurse specialists skilled in all aspects of epilepsy care should be available.

Management of sodium valproate in pregnancy
While clinicians might consider valproate withdrawal or switching to an alternative antiseizure medication during pregnancy, this can be practically difficult and present a risk of worsening seizures. The potential for valproate withdrawal causing seizure exacerbation
should be presented to patients. There is a doubling of the risk of bilateral convulsive seizures when valproate is withdrawn (33%; n=93), or replaced (29%; n=38) in pregnancy, compared with those maintained on it (16%; n=1588). 60,61

Where valproate withdrawal is deemed unsafe, patients may consider changing to the prolonged release preparation and fractionating the dose to reduce peak valproate serum concentrations. While the impact of this change on the risk of major congenital malformations in human pregnancies is less clear, and the effect on neurodevelopment is unknown, many consider this approach in practice.

Perinatal management
Most women with epilepsy will have an uncomplicated vaginal delivery. The incidence of seizures during delivery is around 1%–3%.57 One-to-one perinatal care should be available. Delivering mothers need to remain hydrated, receive adequate analgesia and have their usual antiseizure medications on time.

Any seizures should be terminated as quickly as possible to minimise maternal and fetal hypoxia. Seizures should be managed, as is usual practice, for status epilepticus. Where pre-eclampsia or eclampsia is anticipated or encountered, management should follow obstetric recommendations using intravenous magnesium sulfate.

As for all newborns, infants should receive 1 mg vitamin K intramuscularly to prevent haemorrhagic disease of the newborn.57

Postpartum management
Serum concentrations of antiseizure medications revert to pre-pregnancy levels usually within 2 weeks after birth. If the dose of an antiseizure medication has been increased during pregnancy, therapeutic drug monitoring might be considered to predict potential toxicity, although steady-state level cannot be inferred with the rapid changes in clearance in the early postpartum period. Clinicians may consider empirical reductions towards pre-pregnancy doses, with dose reductions every 2–3 days as necessary over the first two postpartum weeks. The decision to return to pre-pregnancy doses should be made on an individual basis. If the increase has resulted in a sustained improvement in seizure control, without signs of postpartum toxicity, then the dose may be left unchanged.

The risk of injury to an infant during maternal seizures depends on seizure type and frequency. This can be minimised if mothers with epilepsy are given advice on safe handling, bathing techniques, breast feeding and safe practice around the home.

As with the general population, women should be encouraged to breast feed where this is possible. Antiseizure medications are secreted in breast milk in concentrations inversely proportional to the extent of maternal serum protein binding. Barbiturates, benzodiazepines, lamotrigine, zonisamide, levetiracetam and ethosuximide have been associated with lethargy and irritability requiring mothers to stop breast feeding. There are generally no issues for most antiseizure medications, although we still have limited information on some of the newer medications’ content in breast milk. Combined breast feeding and bottle feeding may help reduce medication exposure if this is of concern. For women taking valproate, the evidence is reassuring. At age 6 years, breastfed children, including those exposed to valproate, had higher IQ and enhanced verbal and non-verbal memory and executive functioning compared with non-breastfed infants.52

Key points

► The dangers of convulsive seizures require us to identify women at higher risk of seizures during pregnancy: those with seizures in the year before pregnancy; those taking more antiseizure medications; and those taking lamotrigine monotherapy.

► Clinicians should discuss the risks of antiseizure medications in pregnancy early and often, while noting the risks of stopping them suddenly.

► Women with epilepsy who are contemplating pregnancy should use the lowest effective dose of antiseizure medication and avoid those medications most associated with fetal harm.

► For women of reproductive age, at each clinic visit, clinicians should offer a discussion around individual risks and treatment during future pregnancies.

► Managing the dose of antiseizure medications during pregnancy requires a recognition of the delicate balance of managing seizure risk and the risks of teratogenicity and cognitive change, and involves a shared decision-making discussion.

► Decisions on therapeutic drug monitoring during pregnancy should be made as early as possible.

Further reading


Depression and anxiety are important postpartum issues, including in women with epilepsy, who are prone to peripartum and postpartum exacerbations of psychiatric conditions.63 64 Women with epilepsy are less likely to receive specific treatment compared with controls, probably due to fears of treatment exacerbating seizures. Suicide risk should be considered, given its threefold increase in those with epilepsy.65

The MBRACE report from 20213 showed a continued sustained rise in SUDEP risk during the year after delivery. Mothers should be counselled on the need for good adherence to antiseizure medications and preservation of healthy sleep patterns, where possible enlisting support from family. As with all patients, risk factors for SUDEP should be identified and appropriate counselling provided.

CONCLUSION
With adequate care and planning, the risks to mother and baby posed by epilepsy and its treatment can often be foreseen and mitigated. Pregnancy-specific epilepsy education should begin in the teenage years. Care during pregnancy should include follow-up at least once in each trimester by someone skilled in managing epilepsy, and this should extend into the postpartum year. Many pregnancies are unplanned, and discussion of pregnancy-related information should ideally begin at the time of epilepsy diagnosis in women of reproductive age. Modification of epilepsy treatment and obstetric management should take the mother’s preferences into account. Provision of appropriate information may help maintain the mother’s confidence and enhance adherence with plans and schedules during pregnancy.

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