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Epilepsy in pregnancy

A collaborative team effort of obstetricians, neurologists and primary care physicians for a successful outcome

Background

Epilepsy is the most commonly encountered serious neurological problem in obstetrical practice. The disease and treating medications may have significant impact on contraceptive choice, efficacy and reproduction.

Objective

This article seeks to inform general practitioners (GPs) about current developments in the field of pregnancy care for women with epilepsy and to foster a collaborative approach in their management.

Discussion

The care of a pregnant woman with epilepsy needs to start well before pregnancy occurs, while she is still under the care of a GP, especially if she is on antiepileptic medication. GPs are familiar with the concept of GP management plans and team care arrangements for chronic diseases. This model of team care should be extended to the management of women with epilepsy with regards to reproduction. It is hoped this will enhance perinatal outcomes for women and their infants by encouraging shared communication between the obstetrician, neurologist and GP.

Keywords

obstetrics, pregnancy; epilepsy; medication therapy management; medical care team



Epilepsy is the most commonly encountered serious neurological problem in obstetrical practice. The incidence of epilepsy is 0.3–0.5% in different populations around the world.¹ The proportion of the population on antiepileptic drugs (AEDs) ranges from 4–9 per 1000 people.² In Australia, approximately 1500–2000 women on AEDs become pregnant each year.³ There are widespread concerns about the teratogenic risks posed by AEDs. The disease and these medications may have significant impact on reproductive function, contraceptive choice and efficacy. During pregnancy, the obstetricians, neurologists and primary care physicians have the unenviable task of ensuring freedom from seizures during pregnancy while minimising possible adverse effects of AEDs on the fetus and maximising the opportunity for a good outcome for the mother and the newborn. The purpose of this article is to provide an update on management of women with epilepsy before and during pregnancy, and in the postpartum period, paying particular attention to the areas where GP care is involved.

Preconception care

Epilepsy is not a contraindication for pregnancy. More than 95% of pregnant women with epilepsy deliver a healthy baby, even under medical treatment.⁴ It is important to reassure women about the probability of a good outcome, but it is also crucial to provide preconception counselling, focusing on optimisation of AEDs, folic acid supplementation and contraception to prevent unplanned pregnancy and minimise the risk of complications. Awareness of these issues remains poor despite the recommendation by NICE⁵ for this to be conducted for all women with epilepsy of childbearing potential. A recent study found that only 46% of women with epilepsy recalled being provided with information on the interactions between AEDs and contraceptives, 63% on the need to plan pregnancies and only 56% on the need for folic acid supplementation.⁶

Reproductive function and fertility in women with epilepsy

There have been reports of increased rates of sexual dysfunction, hypothalamic amenorrhoea, hyperprolactinaemia, premature menopause,



increase in anovulatory cycles and polycystic ovarian syndrome (PCOS) in women with epilepsy.⁷ Fertility is also reported to be lower in women with epilepsy, although a recent Scandinavian population-based cohort study⁸ suggests the impact is modest. The birth rate was lower in women with epilepsy than in those without epilepsy (hazard ratio 0.83, 95% CI 0.83–0.93).⁸

Contraception

Women with epilepsy should be aware that hormonal contraceptive failure may occur with enzyme-inducing AEDs (EIAEDs) such as phenobarbitone, primidone, phenytoin, carbamazepine, oxcarbazepine, felbamate and topiramate. They induce the hepatic cytochrome P-450 enzyme system and increase the clearance of contraceptive steroid while increasing the level of sex hormone-binding globulin, which in turn decreases the levels of freely circulating progestins.⁹ Hormonal contraceptive efficacy is unaffected by non-EIAEDs, such as valproic acid (VPA), zonisamide, benzodiazepines, gabapentin, levetiracetam, pregabalin, tiagabine and vigabatrin.⁹ Where use of the combined oral contraceptive pill (COCP) is necessary, a higher oestrogen dose COCP (eg. 50 µg ethinyl oestradiol) has traditionally been recommended.¹⁰ Alternative preferred methods are depomedroxyprogesterone acetate (DMPA), a levonorgestrel-releasing intrauterine contraceptive device (Mirena) or barrier methods for women with epilepsy taking EIAEDs. Administration of high dose DMPA continues to provide effective contraception in women taking hepatic EIAEDs; however, some authorities suggest administering DMPA every 10 weeks rather than 12 weeks.^{10,11}

Recent studies suggest that administration of COCPs increases the metabolism of lamotrigine (through increased glucuronidation), reducing levels by approximately 50%, and has also been associated with a significant worsening of seizure control.¹² An increase in lamotrigine dose is therefore required when commencing the COCP and appropriately reducing the dose on cessation.¹³

The levonorgestrel-releasing intrauterine contraceptive device is a highly effective form of contraception as the progesterone effect is mediated locally and is less affected by the EIAEDs.⁹ Given that it is both reversible and highly effective, and has an estimated failure rate of 1% among these women, a levonorgestrel-releasing intrauterine contraceptive device has been suggested as the first-line contraceptive choice for women with epilepsy using EIAEDs¹¹ or lamotrigine.¹³

EIAEDs cause a reduction in circulating levels of levonorgestrel, which makes low dose (or mini-pill) progestin-only pills unsuitable for use in women who are on EIAEDs.^{11,13} The contraceptive efficacy of levonorgestrel or etonogestrel implants has also been reported to be reduced in women taking EIAED, resulting in the recommendation that this form of contraception be avoided among women taking EIAEDs.^{11,13,14}

Choosing an AED for women of reproductive age

The risk of congenital malformation is higher in women with epilepsy. In an effort to better quantify the risk of treated versus untreated epilepsy, a Finnish population-based study¹⁵ has compared the risk of major

malformation in women with epilepsy, with and without treatment. This study confirmed that major congenital malformations were more common among women on AEDs (4.6%) than among untreated patients with epilepsy (2.8%).¹⁵ This finding is also consistent with a recent study by Vajda et al¹⁶ showing AED exposure during pregnancy was associated with 6.5% of congenital fetal malformations (CFMs), whereas no exposure to AEDs was associated with 3.2% of CFMs. The pathogenesis of fetal malformations is likely to be multifactorial even for women on AEDs. In addition to the direct effect of AEDs, there may be contributions from toxic AED metabolites, reduced folate availability, hypoxic injury associated with seizures, and genetic predisposition.¹⁷

As a single agent, VPA consistently has the highest rate of malformations.¹⁸ At doses above 1100 mg/day, VPA has been found to be associated with a significantly higher incidence of CFMs than other AEDs ($P < 0.05$).¹⁸ The North American AED Pregnancy Registry¹⁹ showed that between 1997 and 2011, the risk of major malformations was 9.3% for VPA, 5.5% for phenobarbitone, 4.2% for topiramate, 3.0% for carbamazepine, 2.9% for phenytoin, 2.4% for levetiracetam and 2.0% for lamotrigine. VPA was associated with a higher risk of neural tube defects, hypospadias, cardiac defects and oral clefts; phenobarbitone was associated with a higher risk of cardiac defects and oral clefts; topiramate was associated with an increased risk of cleft lip, compared with that of a reference population. The results of this analysis also found that AED groups with higher frequency of seizures during pregnancy had lower risk of malformations.¹⁹

Because of the association between VPA and CFMs, confirmed by pregnancy registries all over the world, the American Academy of Neurology recommended avoidance of VPA during pregnancy whenever possible. The safety data on the newer AEDs is limited. The risk of malformation with polytherapy is higher than with monotherapy. A meta-analysis by Meador et al²⁰ reported a significantly higher rate (9.84%) of CFMs for polytherapy than for monotherapy (5.3%).

There has been increasing concern regarding the potential adverse effect of AEDs on fetal cognitive development. The risk of structural malformations is essentially confined to the first trimester, whereas effects of AEDs on cognitive development can occur throughout gestation. In a large-scale population-based study on early developmental outcomes in offspring of parents with epilepsy, exposure to AEDs during pregnancy was associated with adverse development (gross motor skills, sentence skills, autistic traits) at 18 and 36 months of age.²¹ The NEAD follow-up study at 6 years showed that fetal exposure to VPA has dose-dependent associations with reduced cognitive abilities across a range of domains at 6 years of age.²² An investigation by Christensen et al²³ provides the strongest evidence to date that fetal exposure to VPA is associated with increased risks of autism and autism spectrum disorder.

In a recent Australian study,¹⁶ neurologists prescribed VPA less frequently and in smaller doses than did other classes of practitioner (such as GP, psychiatrists) over a 10-year study period. There was a parallel decrease in the occurrence of fetal malformations in pregnancies referred to the register by neurologists, whereas other prescribers seemed to have adopted these practices to a lesser extent.



Recent evidence suggests no greater risk of major congenital malformations (MCMs) associated with lamotrigine when compared with untreated pregnancies in women with epilepsy.¹⁸ Although lamotrigine monotherapy was not associated with MCMs, in one study it was associated with the loss of two babies after status epilepticus or prolonged seizures after VPA withdrawal and replacement with lamotrigine.¹⁸ It is therefore important to balance a lower risk of association with teratogenic outcomes against efficacy in controlling seizures. The aim should be to have seizure control for at least 6 months before conception and, if possible, cease or use the lowest effective dose of a single anticonvulsant according to the type of epilepsy.¹⁰ Medications should be taken in divided doses, avoiding high peak levels, and once pregnancy is established, medications should not be changed. Women with epilepsy who are contemplating pregnancy should also be advised to have 5 mg of folic acid/day for at least 1 month before conception and throughout the first trimester.¹⁰

Pregnancy care

Women with epilepsy in pregnancy should be seen by obstetricians and neurologists in a multidisciplinary team environment. Obstetricians caring for women with epilepsy need to consider the likely impact of pregnancy on seizure frequency, the potential impact of epilepsy on obstetric outcomes, the role of monitoring AEDs levels, surveillance for congenital malformations, continuation of folic acid supplements and the place of vitamin K supplementation. Women with epilepsy should be encouraged to register in the Australian Pregnancy Registrar (APR) of AEDs.

Effects of pregnancy on epilepsy

For most women with epilepsy, the frequency of seizures does not increase during pregnancy. The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) reported in 2006 on 1882 women with epilepsy whose seizure control and treatment was prospectively recorded; 58% of participants were seizure-free during pregnancy; seizure frequency and AED treatment remained unchanged in 62–64%.²⁴ The APR also found that pregnancy had little impact on seizure frequency among treated women. A 12-month seizure-free period before pregnancy was associated with a 50–70% reduction in seizure risk during pregnancy. Many women who experience increased seizure frequency are sleep-deprived or noncompliant because of concerns about the effects of the medication on the developing fetus. Altered AED pharmacokinetics may also contribute to change in seizure frequency during pregnancy.

Effect of epilepsy on obstetric outcomes

The impact of epilepsy on obstetric outcome seems modest. A number of obstetrical complications are reported to be more common in women with epilepsy; these range from mild to severe, and include a low birth weight, lower Apgar scores, pre-eclampsia, bleeding, placental abruption and prematurity. However, the evidence associating many of these complications with epilepsy is limited and was considered inconclusive in a 2009 systematic review.²⁵

Effect of epilepsy on the fetus

In addition to concerns about fetal exposure to AEDs, there are risks to the fetus from maternal seizures and maternal epilepsy. It is important to reassure women who do not require AEDs that they are not at increased risk of having a baby with a birth defect. Although the fetus is relatively resistant to short hypoxic episodes, prolonged convulsive seizures may result in sustained fetal hypoxia. Protecting the fetus from the consequences of frequent or sustained seizures is a compelling argument for maintaining AED use during pregnancy. Additional risks of maternal seizures include injury to the fetus, abruption or miscarriage due to maternal trauma sustained during a seizure. There is about a 4-fold increase in the risk of epilepsy in infants of women with epilepsy.²⁶

AED levels and dose adjustment

The pharmacokinetics of AEDs may be significantly altered in pregnancy by changes in body weight and effects on drug absorption, protein binding, metabolism and excretion. Serum concentrations of older AEDs such as phenobarbitone, primidone, carbamazepine, phenytoin and VPA have been shown to be decreased in pregnancy.²⁷ In women with epilepsy, the goal of therapy is to maintain seizure control using the lowest effective AED dose. The International League against Epilepsy position paper recommends that drug concentrations be determined during pregnancy. For patients with good control, serum concentration should be assessed each trimester, but more frequent assessment may be required in patients with complicated epilepsy.

Surveillance for birth defects

In women with epilepsy, especially those taking AEDs, an ultrasound examination at 11–13 weeks should be offered. If acrania (the precursor of anencephaly) or increased nuchal translucency (useful screening test for cardiac and other structural defects) is found, an early referral should be made to the obstetrician. At mid-pregnancy, an expert morphological assessment should be performed. Notes on the history of the epilepsy and the medication regimen should be made on the referral so that a targeted assessment, particularly of the neural axis, heart and face, can be performed.

Folic acid supplementation

While there is a range of views about the actual value of folate as a supplement, it seems to be of benefit for healthy women in preventing malformations. The 2009 American Academy of Neurology and American Epilepsy Society guidelines state that data are insufficient to determine whether doses higher than 0.4 mg offer greater protective benefits. In contrast, the American College of Obstetricians and Gynecologists recommend 4.0 mg of folic acid daily for women at risk of having offspring with neural tube defects (including women taking AEDs).

Vitamin K supplementation

Another controversial issue is whether AEDs increase the risk of haemorrhagic disease in newborns. Several case control studies have challenged the previous recommendation of vitamin K administration



in late pregnancy after observing no increase in bleeding complications between neonates born to women with epilepsy receiving EIAEDs and healthy controls. The findings of these studies have formed the basis of some consensus statements (for example, the NICE guidelines⁵) that no longer recommend vitamin K supplementation for women with epilepsy receiving EIAEDs in late pregnancy, but rather administration of phytomenadione to the neonate.

Intrapartum care

There is increased risk of seizure recurrence in labour and delivery. The reasons for this are multifactorial and include poor bioavailability of AEDs, compliance, sleep deprivation, anxiety and hyperventilation during labour. The EURAP registry reported that seizures occur in 60/1956 (3.5%) of women with epilepsy in labour.²⁴ Therefore, women should deliver in a centre with adequate facilities for maternal and neonatal resuscitation. Most women with epilepsy are able to undergo normal vaginal delivery. An intravenous access should be secured during labour, in anticipation of a seizure, and AEDs should be continued. Attention should be paid to avoid hyperventilation and maternal exhaustion. In case of generalised tonic-clonic seizures, a continuous CTG tracing should be performed. There should be readiness to deal with any seizure activity; intravenous benzodiazepine (eg. lorazepam or diazepam) is recommended for seizure termination.

Postpartum care

Women should be seen by the neurologist to adjust the AED dose. Maternal plasma levels of AEDs may fluctuate up until the eighth postpartum week and monitoring of plasma AED levels may be required. AED requirement is likely to fall in the puerperium and toxicity may occur if the dose is not adjusted. Lamotrigine and oxcarbazepine doses in particular may need to be reduced postpartum.

All AEDs are secreted in the mother's milk; the newer AEDs are found in higher concentrations than the older ones.²⁸ The benefits of breastfeeding must be balanced against the possible adverse effects of AEDs in the baby. It may be preferable for mothers taking lamotrigine and levetiracetam to abstain from breastfeeding.

Appropriate counselling for contraception and advice regarding minimising the risk of seizures at home should be given to the woman and her family. This involves reinforcing the importance of medication compliance and adequate sleep. Minimising any risk of injury to the baby can be accomplished by sitting close to or on the floor while feeding the baby, bathing the baby with another person present whenever possible, minimising carrying the baby, and using a pram with an automatic brake.

Key points

Preconception care

- Counselling that most women with epilepsy will have a good outcome
- Increased risk of congenital malformation with AEDs
- Avoidance of VPA, particularly doses of >1100mg/day, and switching to a suitable alternative if possible
- Aim for the lowest effective dose of a single anticonvulsant

- Ensuring effective contraception until seizure control is achieved (higher dose of COCP, DMPA, or a levonorgestrel-releasing intrauterine contraceptive device)
- High dose folic acid supplementation for at least 1 month before conception and aiming to continue through first trimester

Pregnancy and delivery care

- No change in AEDs after pregnancy occurs
- Encouragement to register with APR (telephone: 1800 069 722)
- Offer ultrasound scans at 11–13 weeks and expert morphology ultrasound scans at 18–20 weeks
- Monitor serum levels of AEDs at least once in each trimester
- Vigilance of increase seizure frequency in labour and delivery
- Terminate epileptic seizures using intravenous benzodiazepine

Postpartum care

- Monitoring and adjusting AED level if necessary
- Most AEDs are excreted in the breast milk; benefits of breastfeeding should be considered against the possible adverse effects of AEDs on the newborn
- Discharge counselling with advice of harm minimisation for mother and baby
- Best contraception advice

Conclusion

While managing a pregnant woman with epilepsy, general practitioners play a pivotal part in the three-way communication that occurs between the obstetrician, neurologist and themselves. It is therefore necessary to have up-to-date information about the disease and its management during pregnancy. With the advent of pregnancy AED registries and landmark research studies, information is available regarding various AEDs, their effects on the fetus, and harm minimisation without compromising maternal health.

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Competing interests: None.

Provenance and peer review: Commissioned; externally peer reviewed.

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