

Managing pregnancy in women with epilepsy

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In this highly informative article, Director and Principal Investigator of the Australian Pregnancy Register at Monash University, Professor Frank Vajda, discusses the role of pregnancy registers and passes on a number of considered observations to help address some of the many questions people have about the possible impact of epilepsy and epilepsy treatment on pregnancy.

Summary

The role of Pregnancy Registers is to assess the risks to babies exposed to antiepileptic drugs (AEDs), to compare the efficacy of various drugs, and to observe possible improvements in management practice over time. Registers are a controlled, prospective or forward looking way to collect data related to the outcome of pregnancies in women with epilepsy, to study the natural history of the condition and seizure control, comparing all the factors such as type of epilepsy, other drugs and illnesses, and social and environmental factors. The vast majority of birth outcomes in women with epilepsy result in normal babies. Seizure control in women with epilepsy must be balanced against risk of foetal exposure to the potentially adverse effects of antiepileptic drugs. The most appropriate drug must be used to treat each woman with epilepsy, even before they become pregnant.

Management of Epilepsy in Pregnancy

The clinical diagnosis of epilepsy is made on the basis of eyewitness accounts supported by tests, including EEG [electroencephalogram], imaging with CT [computerised tomography] or MRI scan [magnetic resonance imaging technology], and possibly video monitoring. It is important at this time that other diagnoses, which may be mistaken for epilepsy be excluded.

These are often related to simple syncope or faint which can occur following a sudden loss of muscle

tone related to a lowering of blood pressure or changes in heart rhythm, or even non organic events due to emotional problems. These events are not uncommon. In order to treat and appropriately manage epilepsy an accurate assessment of the type of epilepsy (the so-called 'syndrome') needs to be made.

Counselling

Women of childbearing age should be given an early explanation about epilepsy and its possible impact on having children, and whether there is a

risk of inheriting an epileptic tendency. A healthy normal baby can be expected in 95 per cent of pregnancies in women with epilepsy, treated with antiepileptic medications.

Women who do not take AED's while pregnant will obviously have less risk of adverse effects from AED's but they will also have a far greater risk of experiencing seizures during their pregnancy which in turn can cause harm to both the mother and her baby.

Advice on avoiding becoming over-tired, use of alcohol, minimising stress and taking folic acid at 5 -10 mg per day

before pregnancy occurs should be included in the counselling.

While there are a range of views about the actual value of folate as a supplement, it appears to benefit healthy women in preventing malformations.

The results in epilepsy are less definite in terms of its protective value but it is unlikely to cause harm and may confer some benefit.

Monitoring

It is a sound practice to have an early ultrasound examination to establish the date of pregnancy, and then a further ultrasound at 13 weeks. These are desirable to exclude major malformations.

Plasma AED level measurements are not routinely employed, but may be done for mothers taking lamotrigine, which is affected by sex hormones. Both the “pill” and pregnancy increase lamotrigine elimination and whatever dose of lamotrigine that is being taken becomes less effective.

Lamotrigine doses may be increased in each term of pregnancy but then reduced after delivery of the baby as levels then rise and may cause adverse effects.

Which drug?

A woman of childbearing age should be treated with the best drug for her type of epilepsy.

i. The currently accepted first choice of drugs for generalised epilepsy is not based on results of extensive randomised clinical trials, or ‘first-class evidence’.

As these studies are not available, less perfect, clinical evidence suggests using valproic acid as first-line monotherapy in primary generalised epilepsy, and lamotrigine or topiramate as second line alternatives. Although lamotrigine may be safer, it may not be as effective as valproate.

Valproic acid (Epilim) controls all manifestations and does not cause seizure aggravation, nor produce other seizure types. For some syndromes such as juvenile myoclonic epilepsy, valproic acid is clearly more effective than lamotrigine, but its teratogenic potential in pregnancy – in other words its potential to lead to foetal abnormalities – at high doses, poses a higher risk than other drugs.

The evidence comparing medications currently is largely drawn from clinical experience gleaned over decades. Dismissing compelling clinical anecdotal evidence is unwise, as the results of clinical trials are not directly reproduced in a clinical setting. Many drugs which perform well in trials, fail when used in large populations.

ii. A wider choice of drugs is available for treating focal or partial epilepsy, Carbamazepine (Tegretol) is accepted as the first-line drug, although oxcarbazepine (Trileptal), tiagabine (Gabitril), levetiracetam (Keppra), gabapentin (Neurontin), topiramate (Topamax), and lamotrigine (Lamictal) may all be effective.

However, evidence for their foetal safety in pregnancy is not yet firmly documented as these new drugs have not been tested in sufficient number of patients. Phenytoin (Dilantin) and phenobarbitone are no longer considered first-line treatment, although still used.

Considerations for first-choice AEDs, apart from efficacy and safety, include cost, tolerability and adverse effects. Treatment should be started slowly and titrated – brought to the right level gradually, especially with lamotrigine, which may take 8 weeks to stabilise.

Other considerations include weight gain with valproic acid or weight loss with topiramate.

In epileptic women of childbearing age, multiple drug treatment should be avoided, if possible. Medications should be taken in divided doses, avoiding high peak levels, and once pregnancy is established, medications should not be changed.

The occurrence of pregnancy in a woman of childbearing age should be anticipated

The question of changing medication for women during pregnancy arises only if her epilepsy has not been well managed prior to the pregnancy. There may also be a fear of adverse effects of drugs on the baby. So far only high dose valproate and phenobarbitone have shown a higher than acceptable risk.

Many pregnancies are unplanned. By the time a woman discovers she is pregnant, her pregnancy may have reached the middle of the first 13 week term. To change medication at this time

may cause additional seizures.

Many women have long periods of seizure freedom in pregnancy. This may possibly be a favourable time to consider withdrawal of medication, but the risk of further seizures, and the risk of SUDEP (sudden unexpected death in epilepsy) make many authorities seriously doubt that withdrawal of medication is safe, although it may be regarded favourable for the foetal outcome, but only in carefully elected cases, who do not have convulsive seizures.

Childbirth

Most women with epilepsy are able to undergo natural, vaginal delivery. They may have local anaesthesia, a so called “peridural” to relieve pain.

An intravenous line may be made available to administer clonazepam (Rivotril) or midazolam to abort seizures in case they were to occur during childbirth. The foetus must be monitored to prevent respiratory complications.

Breastfeeding

All AEDs are secreted in the mother’s milk. Newer AEDs and are found in higher concentrations in human milk. The benefits of breastfeeding must be balanced against the adverse effects of AED exposure to the baby. Routine monitoring of lamotrigine, which is high in breast milk, is difficult. It may be preferable for mothers taking lamotrigine to abstain from breastfeeding. Levetiracetam is excreted in large quantities in milk, not favouring breastfeeding. Adverse respiratory effects with benzodiazepines and phenobarbitone have been reported, suggesting that these drugs may be contraindicated in breastfeeding.

Epilepsy and malformations in the baby

A number of studies show that the type and frequency of seizures may be unrelated to major malformations in the baby. One study found a lower verbal intelligence in children whose mother had more than five generalised seizures during pregnancy. There are some patients with epilepsy, who are highly susceptible to foetal malformations when the foetus is exposed to an AED. Evidence supporting this comes from families where several offspring have

had malformations on the same drug.

The risk of foetal malformations in relation to AED exposure is two- to three-fold that of the general population but this needs to be kept in perspective in that malformations in the general population are not common.

Pregnancy registers, supported by the International League Against Epilepsy, were established to provide prospective information on the causation of malformation. It is estimated that 5,000 patients are required to be exposed to monotherapy for each AED before the relative risks of foetal malformations can be established.

These Registers operate on a basis of strict protocols, prospective enrollments, hospital ethical approval and patient consent. Telephone interviews are used for collection of relevant personal and medical data. Progress reports are published periodically.

They do not immediately benefit expectant mothers with their current pregnancy although they have already shed light on a number of matters which offer the possibility of better pregnancy management.

Their applicability to a population depends on how representative they are of the overall pool of expectant mothers at any time. It may be that only the better informed, economically better off and more alert patients are willing to participate. There may be a selection bias. Women under specialist neurological care are more likely to be advised to enroll in a Register. The registers are observational only.

Company related pregnancy registers include gabapentin, topiramate and lamotrigine related projects. The lamotrigine register is the largest. Its initial results suggest that polytherapy in pregnancy involving a combination of lamotrigine with valproate may be more teratogenic than lamotrigine monotherapy, or polytherapy involving lamotrigine with AEDs other than valproate. There may be a number of possible explanations, which are yet unexplored.

Results from the Australian Register

The Australian Register compared the efficacy of the most widely used AEDs, valproate, carbamazepine and

lamotrigine, throughout pregnancy. Although the study was not randomised to measure seizure protection, patients treated with valproate appeared more effectively protected from seizures of all types than patients prescribed lamotrigine.

It was noted however that valproic acid-related malformations occurred statistically significantly higher at or above 1,100 mg per day in monotherapy.

The daily dose of valproic acid used in relation to foetal malformations is important. Samren et al found a relative risk of 7 in women taking more than 1,000 mg/day of valproic acid daily. Higher valproic acid plasma concentrations were noted in women bearing children with foetal malformations than in women with epilepsy whose children had been born without any malformations. Recent retrospective extensive data on older drugs involving over 20,000 patients from Finland also indicate that valproic acid is associated with a higher risk of foetal malformations than other older AEDs.

The newer AEDs are not yet recommended for women at childbearing age, as insufficient is known about their foetal safety. Some changes in prescribing trends have also been observed – possibly as a result of education – the usage of high-dose valproic acid has been reduced in Australia. Prospective studies have not yet demonstrated a link between the type of malformation with a specific AED. There is as yet no evidence of a significant difference in the incidence of malformations in offspring exposed to a single older AEDs, such as phenytoin and carbamazepine, with the exception of phenobarbitone which has fallen largely into disuse, and valproic acid above 1,100 mg per day,

Intellectual slowing

The risk of cognitive impairment associated with epilepsy and AED exposure has been studied only retrospectively and there is a suggestion that exposure to valproate may be adverse compared to other drugs.

Further studies are needed to define dose-relationships and the critical time of exposure. Offspring must be followed up for several years to measure the

extent of cognitive challenge.

What can we advise ?

We can provide women with epilepsy with the available information, advise on the best treatment prior to pregnancy, and warnings that most AEDs carry a risk above that of untreated epilepsy. Treatment should be planned in women anticipating pregnancy.

Valproate, especially in doses above 1100 mg per day, has been shown to be associated with a higher level of risk. This has to be balanced against its effectiveness. Changes in AED regimes may risk upsetting seizure control and may also expose the foetus to periods of polytherapy.

If lamotrigine or another AED is to be used in the first trimester, the treatment must be started before pregnancy is established, as the major risk to the foetus occurs in the first trimester, when the baby's organs are formed. Tests should be carried out to rule out malformation.

Multiple drug therapy should be avoided – if possible – and drugs should be given in divided doses to avoid high peak levels.

Despite a lack of firm evidence that it is effective in epilepsy, pre-conception administration of folate is nonetheless recommended.

Intellectual and behavioral changes and unusual facial features may be due to longer term *in utero* exposure to AEDs. This alone may justify a possible switching of medication, but evidence for these complications has not yet been confirmed.

References

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