Pregnancy and epilepsy
balancing the risks

Excellent pregnancy outcomes for mother and child occur in more than 90% of the women with epilepsy who choose to become pregnant, but there are some specific health risks to both mother and child that need to be appreciated and controlled as much as possible.

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Women with epilepsy have particular problems of management due to biologically determined differences from their male counterparts. Female sex hormones may specifically alter the frequency of epilepsy and the metabolism of anticonvulsant medication. Other difficulties lie in the area of reproduction.

Epilepsy control may become more uncertain and many or all of the currently used anticonvulsant drugs seem to have the potential to cause abnormality of fetal structure and/or abnormal development *in utero*. There is little or no specific information on the newer antiepileptic drugs and the associated pregnancy risks. The degree of risk for each individual anticonvulsant drug or each antiepileptic drug combination used in pregnancy is hard to determine as reproductive women are excluded from clinical drug trials. The information presently available relies on postmarketing reports of fetal abnormality and these are essentially sporadic and uncontrolled.

This paper proposes to briefly examine some of the relevant clinical issues by answering the questions typically posed to a doctor by a potential mother with epilepsy and by providing a practical, contemporary guide to the management of the pregnant woman with epilepsy.

IN SUMMARY

- **Information given in the early years of epilepsy management is very helpful preparation for the time when a pregnancy is desired.**
- **While there is no evidence that simple partial seizures, complex partial seizures or absence seizures result in any increased risk to the fetus, generalised tonic–clonic seizures are potentially harmful to both mother and child. The maternal risk of recurrent generalised seizures (in particular, status epilepticus) is often understated and overlooked in the anxiety to avoid the use of antiepileptic drugs.**
- **Approximately 15 to 30% of women with epilepsy will have an increase in the number of seizures in pregnancy.**
- **In pregnancy, the metabolism of some antiepileptic drugs is altered and their bioavailability is reduced. Monitoring is necessary.**
- **In pregnant women with epilepsy, there may be an increased risk of haemorrhagic disease of the newborn, especially if the mother is taking enzyme-inducing antiepileptic drugs. Therefore, vitamin K supplements are recommended for all neonates.**
- **The single most appropriate antiepileptic drug for the maternal epilepsy should be continued in pregnancy. It seems logical to give more frequent, smaller doses or a slow release preparation to keep the peak drug concentration down.**
- **The benefits of breastfeeding are generally thought to outweigh the risks of drug to the baby.**

Can I have a baby? What are the risks?

It is desirable that any reproductive woman with epilepsy has some knowledge of the potential issues of pregnancy. Information given in the early years of epilepsy management is very helpful preparation for the time when a pregnancy is desired. For the couple planning a pregnancy, counselling emphasises what is effectively a balance of risks: the possible risks to the mother and her epilepsy, and the risks to the child (Table).

Risks to the mother

Are seizures in pregnancy harmful?

Although there is no evidence that simple partial seizures, complex partial seizures or absence seizures result in any increased risk to the fetus, the person with epilepsy's life is greatly disrupted by these seizures and control is desirable though often difficult.

In contrast, generalised tonic–clonic seizures are potentially harmful to both mother and child. The maternal risk of recurrent generalised seizures (in particular, status epilepticus) is often understated and overlooked in the anxiety to avoid the use of antiepileptic drugs.

Will I have more seizures in pregnancy?

Approximately 15 to 30% of women with epilepsy will have an increase in the number of seizures in pregnancy. This has been attributed in large part to alterations in hormone concentrations resulting in changes in antiepileptic drug metabolism but it clearly also raises issues of compliance, changes in sleep patterns and other contributing factors, such as anxiety.

Will I need more medication?

There are marked changes in the metabolism of some antiepileptic drugs in pregnancy leading to reduced bioavailability and reduced total drug levels. Drugs affected include:

- phenytoin (Dilantin)
- phenobarbitone and its analogues
- carbamazepine (Carbium, Tegretol, Teril), to a lesser degree.

These drugs will require regular monitoring throughout pregnancy and may require dose adjustment if epilepsy control is to be maintained.

There is little or no information about the

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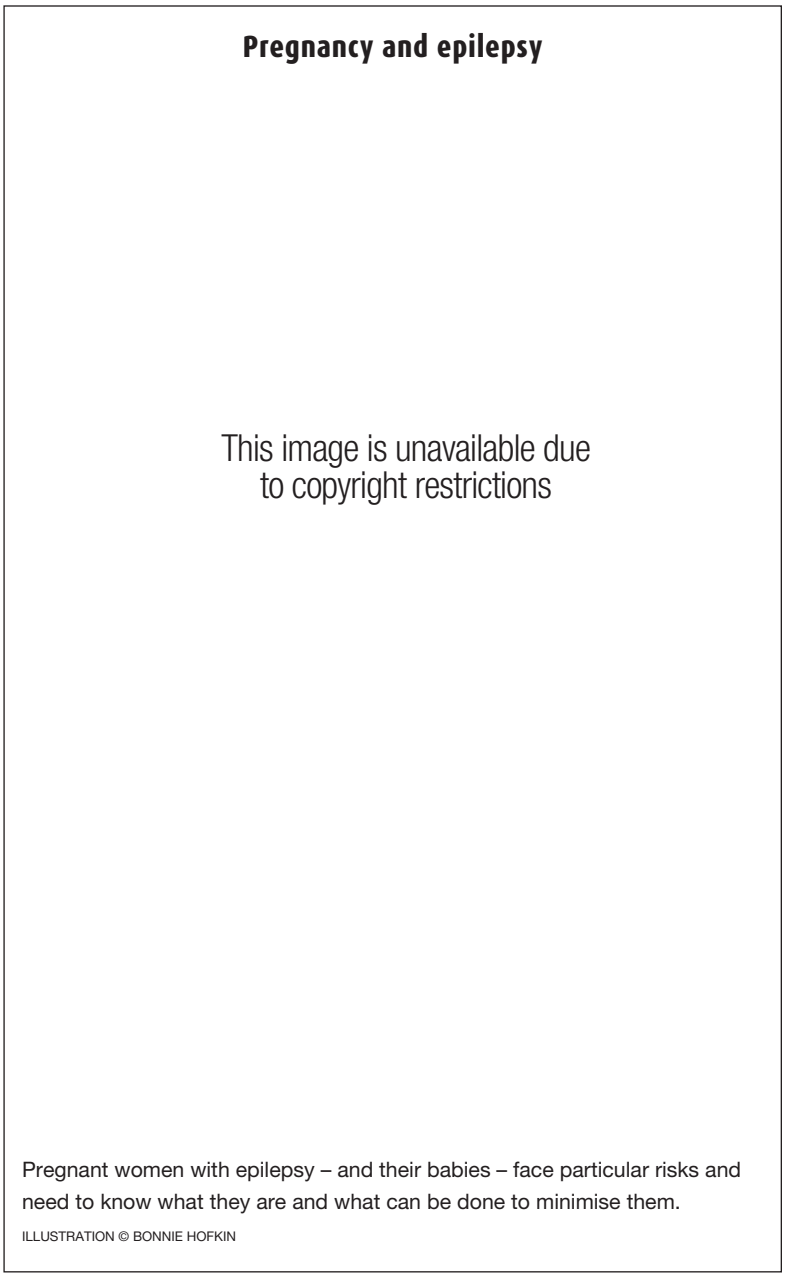

Pregnant women with epilepsy – and their babies – face particular risks and need to know what they are and what can be done to minimise them.

Table. The balance of risks

Risks to the epileptic mother	Risks to the child
Epilepsy	Genetic epilepsy
Death	Preterm delivery or stillbirth
Obstetric issues	Congenital abnormality
	Neurodevelopmental problems

The Australian Pregnancy Register for Women on Antiepileptic Medication

A number of pregnancy registers have been established in North America, Europe and Australia to provide valuable information about the risk of birth defects in women taking specific antiepileptic drugs. In the last five years, a number of new antiepileptic drugs have gained increasing use and the need for direct prospective documentation of pregnancy data and the identification of the lowest risk agents has never been more apparent.

Medical practitioners can assist by recommending that all pregnant epileptic patients register with the voluntary Australian Pregnancy Register for Women on Antiepileptic Medication. For further information, call 1800 069 772 (toll free) or visit the relevant website (www.victorianepilepsycentre.org.au).

metabolism of the newer anticonvulsant drugs in pregnancy.

Are there any other added obstetric risks?

In pregnant women with epilepsy there is a statistically higher risk of:

- vaginal bleeding
- hyperemesis gravidarum
- premature labour and preterm delivery
- forceps- and vacuum-assisted delivery and caesarean section
- stillbirth and perinatal death.

Clearly these complications may be multifactorial and include socioeconomic and associated factors.

Risks to the fetus

Can I lose my baby?

In pregnant women with epilepsy, there may be an increased risk of haemorrhagic disease of the newborn, especially if the mother is taking enzyme-inducing antiepileptic drugs such as barbiturates, phenytoin and carbamazepine. Therefore, vitamin K supplements are recommended for all neonates.

The risk to the fetus of isolated maternal generalised seizures is difficult to establish. Isolated case reports reveal instances of prolonged fetal bradycardia, intrauterine death or miscarriage, and a case of fetal intracerebral haemorrhage after four maternal seizures. However, status epilepticus is known to carry a 30 to 50% risk for fetal death.

Will my baby be normal at birth?

Congenital malformations and anomalies occur about 1.5 to 2.5 times more frequently in children born to women with epilepsy than to women in control populations. Although antiepileptic drug use is probably the major contributor, other pathogenic mechanisms include socioeconomic factors, heredity and possibly maternal seizures in pregnancy. Factors that may increase teratogenic risk include:

- polytherapy with two or more antiepileptic drugs
- high or toxic serum antiepileptic drug levels.

Will my medication affect my baby?

All of the commonly used antiepilepsy drugs (i.e. phenytoin, barbiturates, carbamazepine, benzodiazepines and valproate) have been associated with congenital defects, including cardiac, genitourinary, facial and limb defects. Many of these are also recognised to be associated with a usually mild fetal anticonvulsant syndrome incorporating a pattern of abnormalities including facial dysmorphism and digital abnormalities.

Valproate and carbamazepine have been specifically associated with an increased risk of neural tube defects. Prenatal testing should include serum alphafetoprotein levels at 15 to 18 weeks of gestation and structural ultrasound at 18 to 22 weeks. In some cases, amniocentesis, offering alphafetoprotein and acetylcholinesterase assessment, at 16 to 20 weeks may be indicated.

Virtually nothing is known about the teratogenic potential of the newer antiepileptic drugs such as lamotrigine, gabapentin, vigabatrin, topiramate and tiagabine. At present, there are sporadic and anecdotal case reports as part of postmarketing surveillance requirements. These agents are usually 'add-on' therapy in cases where control of epilepsy has been difficult to achieve or maintain.

Some combinations of antiepileptic drugs may be of greater risk to the fetus than others.

A recent report[1] highlighted the possibility of enhanced risks with:

- carbamazepine–valproate
- caffeine in combination with several antiepileptic drugs, especially phenobarbitone
- benzodiazepine combinations with other antiepileptic drugs, especially valproate and carbamazepine.

It remains to be seen whether these risks will prove to be valid in prospective pregnancy registers (see the box on this page).

The Australian categorisation of the risk of drug use in pregnancy in summarised in the box on page 23.

Will my baby be slow to develop?

A number of reports have suggested neurodevelopmental delay and an increased risk for reduced intelligence in children born to women taking antiepileptic drugs.

For the most part, these reports have been of short term studies and have often failed to consider other aetiological factors, including parental intelligence and heredity issues, socioeconomic status and maternal seizures during pregnancy.

Will my baby have epilepsy?

Most of the primary generalised epilepsy syndromes have a genetic basis and there is considerable potential for a child to inherit this predisposition. Further, it is now recognised that there are some partial epilepsy syndromes (such as benign childhood epilepsy with central temporal spikes [BECTS] and autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE]) that are genetically inherited. Thus, assessment of this potential risk will depend on an accurate categorisation of the maternal epilepsy.

What can we do?

Managing the pregnant woman with epilepsy involves a balance of care for both the expectant mother and the developing child.

Before pregnancy

Preparation

The information about epilepsy and pregnancy outlined earlier in this article should be given, albeit briefly, to every reproductive woman with epilepsy. It should then be given in considerable detail to a couple planning a pregnancy.

Checklist

Six key questions should be asked when managing a woman with epilepsy who is planning a pregnancy. They are listed in the box on page 24 and discussed here. As will be seen, the answer to each key question can prompt further questions.

Does the patient have epilepsy? Is epilepsy the correct diagnosis? Ideally, there will be a definite witnessed seizure and supporting electroencephalogram (EEG) evidence.

If it is epilepsy, is the type (syndrome) known? Does the patient have partial (i.e. focal) epilepsy? If so, what is the cause? (While the commonest pathology is that of mesial sclerosis, other lesions may be present.)

Does the patient have one of the generalised epilepsies? If so, is it primary or is it secondary to a diffuse brain disorder? A recent EEG may be helpful; however, ongoing antiepileptic drug therapy often suppresses the abnormal electrical discharges so that epileptic activity may not be in evidence on investigation. Thus, reviewing earlier EEGs is usually helpful if characterisation of the epilepsy is to be certain.

Is the pathological cause known? A progressive lesion such as a tumour may affect pregnancy outcome. Cause is also relevant when discussing the risk of inherited epilepsy in the child.

Is ongoing drug therapy needed? Generally, the woman with epilepsy should be strongly advised to continue with the medication that controls her epilepsy. A decision to cease therapy should be made only when there has been long term resolution of epileptic events and when the EEG has reverted to normal. However, even when there has been complete seizure control and a normal EEG, there may still be a recurrence of seizures. Social factors such as the woman's need to drive a motor vehicle will influence this decision process.

Is control optimal? The aim is always for complete control of epileptic events. It may be that clinical review indicates a more appropriate medication or dose format. For example, if the woman has primary generalised epilepsy, then the

The risk of drug use of pregnancy

All Australian drug product information indicates categories of risk that have been allocated so that the prescriber can, as far as possible, understand the potential risk of any drug used in pregnancy. The allocation of risk takes the early animal research work into consideration. Table A outlines the categories of risk which are fully discussed in the Australian Drug Evaluation Committee's handbook 'Prescribing medicines in pregnancy'. Table B lists commonly used antiepileptic drugs and their level of risk.

Table A. Australian categorisation of risk of drug use in pregnancy

A		Widely used; no significant risk
B		Limited exposure; no significant events proven in humans
	B1	Animal studies show no significant damage
	B2	Animal studies inadequate or lacking; no damage reported
	B3	Animal studies show fetal damage
C		Pharmacological harm to the fetus; no malformations; harm may or may not be reversible
D		Increased fetal malformations with or without pharmacological harm
X		High risk; avoid in pregnancy

Table B. Risk of antiepileptic drug use in pregnancy

Agent	Level of risk
Carbamazepine	D
Methylphenobarbitone,phenobarbitone, primidone	D
Phenytoin	D
Sodium valproate	D
Benzodiazepines	C
Lamotrigine, tiagabine, topiramate*	B3
Gabapentin*	B1
Vigabatrin*	D

*Compared with the above conventional anticonvulsants, the extent of risk of these drugs is unknown.

epilepsy is most likely to be responsive to valproate (Valpro, Epilim) and lamotrigine (Lamictal). Other medications can be used but usually with less favourable control. If a change in drug management is to be undertaken, this is generally done in overlapping form to avoid withdrawal seizures. The management of each drug is individual, and reference to its metabolic profile and its half-life is essential.

Is the medication being taken in an appropriate dose and form? It is preferable to adopt a medication regimen that allows a smooth dose–concentration curve in order to avoid intermittent toxic serum drug levels. It seems better to give more frequent, yet lower, doses of antiepileptic drugs and also to use slow release preparations when available.

Can polypharmacy be avoided? As detailed earlier (see 'Will my baby be normal at birth?' and 'Will my medication affect my baby?' on page 22), teratogenesis is known to be enhanced by multiple drug usage.

Prophylactic folate

Although there is no direct or prospective evidence available, it seems reasonable to recommend that 1 mg folic acid per day be given to all reproductive women with epilepsy. An increased dose of 5 mg per day should be taken for three months prior to conception and should continue for the duration of the first trimester.

During pregnancy

Pregnant at first presentation

As fetal structural development is virtually complete by the end of the fifth week after conception, there is little purpose in ceasing or changing antiepileptic agents if a women with epilepsy presents during or towards the end of the first trimester.

Monitoring antiepileptic drugs

It is recommended that the single most appropriate antiepileptic drug for the maternal epilepsy be continued in pregnancy. Further, as described earlier, it seems logical to give more frequent, smaller doses or a slow release preparation of an antiepileptic drug in order to keep the peak drug concentration down.

Pregnancy alters the metabolic clearance of many drugs and therefore serum monitoring, every four to six weeks, especially of phenytoin and the barbiturates and to a lesser extent carbamazepine, is recommended as upward adjustment of the dose may be indicated.

Monitoring fetal development

Perinatal monitoring with fetal ultrasound and alphafetoprotein levels at 15 to 20 weeks of gestation can be offered. Clearly this would need to be accompanied with appropriate and sensitive counselling.

After birth

Monitoring antiepileptic drugs

Monitoring of serum drug levels, especially of phenytoin, needs to continue into the postpartum period when downward adjustment of drug dosage may be needed.

Breastfeeding

Antiepileptic drugs are excreted in breast milk in an inverse relationship to their degree of plasma protein binding. Most antiepileptic drugs are not associated with significant problems in the child, although barbiturates may cause substantial sleepiness and feeding difficulties. The level of drug in breast milk is usually considerably lower than that in the maternal serum. The benefits of breastfeeding are generally thought to outweigh the risks of drug to the baby.

Prepregnancy checklist: six key questions

- Does the patient have epilepsy?
- Is the type (syndrome) of epilepsy known?
- Is the pathological cause of epilepsy known?
- Is ongoing drug therapy needed?
- Is control optimal?
- Can polypharmacy be avoided?

Conclusion

Managing the epileptic woman through pregnancy requires time and attention to detail. The process is made difficult by the considerable lack of factual knowledge with respect to the effect of many antiepileptic drugs on the developing child, and pregnancy registers in Australia and overseas may help to address this problem.

A good outcome can be achieved in over 90% of cases but the risks are somewhat higher than for the nonepileptic woman not on medication. For the couple planning a pregnancy, counselling emphasises a balance of risks: the possible risks to the mother and her epilepsy, and the risks to the child. MT

Reference

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Further reading

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