REVIEW

Management of epilepsy in women

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There are many aspects to the management of epilepsy in women related to their role in reproduction. Some of these need to be considered in adolescents, some are related to pregnancy, concerning both the mother and her infant, and others with the menstrual cycle and the menopause. This review considers contraception, fertility, teratogenicity, and the use of folic acid. It also discusses the special investigations in pregnancy, hyperemesis, the effect of pregnancy on the control of epilepsy, the effect of seizures on the fetus, a first fit in pregnancy, pseudoseizures, seizures during delivery, vitamin K, breast feeding, postpartum maternal epilepsy, hereditary risks, counselling, catamenial epilepsy, the menopause, and bone density.

There are special problems in the management of women with epilepsy related to their role in reproduction, which start at the menarche and continue until after the menopause. The prevalence of recurrent epilepsy is about 0.5% of the population and nearly half are women. Maternal epilepsy affects three to four per thousand pregnancies, and epilepsy is the commonest neurological problem in pregnancy. The possibility of pregnancy should be considered in any woman of childbearing age with epilepsy, because treatment is likely to be necessary for a minimum of two years and perhaps indefinitely. This certainly applies to any girl over the age of 15. This topic was the subject of a major review in 1999.[1] Patients may only ask about a few of the following topics at any one time, but most will appreciate a discussion of all the potential problems.[2]

CONTRACEPTION

Q: ''Can I take a contraceptive pill?''

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Combined oral contraceptives (COC)

There is no reason why women with epilepsy taking antiepileptic drugs (AEDs) should not take a COC if they wish to do so after a full discussion of the alternatives. COCs achieve contraception by giving a sufficient dose of oestrogen to inhibit ovulation. The induction of P450 hepatic cytochrome enzyme activity by some AEDs (phenytoin, carbamazepine, oxcarbazepine, phenobarbitone, and primidone) increases the rate of metabolism of both oestrogen and progestogen, thereby lowering the blood concentrations of these drugs, maybe by 50% or more.[3] Topiramate reduces the level of ethinylestradiol by about 30%, but by a different mechanism.[4] Sodium valproate, the benzodiazepines (clobazam and clonazepam), vigabatrin, lamotrigine, gabapentin, tiagabine, levetiracetam, and pregabalin do not affect liver enzyme activity.

It is therefore important to know whether a patient is taking an enzyme inducing AED (EIAED) before prescribing a COC, and to give appropriate advice when prescribing an EIAED to women already taking a COC.

In those women taking an EIAED, start contraception with COC containing at least 50 μg of oestrogen and as the usual seven day pill free interval weakens the contraceptive effect, it is more reliable to tricycle, that is to take three cycles of preparations containing 50–60 μg of oestrogen consecutively, with a shorter pill free interval of four days.[5] If breakthrough bleeding occurs, it usually settles during the first two to three cycles; if not, contraception cannot be assured and the dose of oestrogen may need to be increased.

There is no suitable 50 μg preparation available in the UK. Norinyl-1, which contains 50 μg of mestranol, a prodrug for ethinylestradiol, is not suitable because it is only 75%–80% converted, thus providing less than 40 μg of oestrogen.[6] It is possible to use a 20 and a 30 μg pill, but the oestrogens and progestogens should be compatible,[7] making it easier to use two of the same 30 μg preparation.

As the metabolism of both oestrogen and progestogen is affected, the higher doses of oestrogen should be accompanied by higher doses of progestogen. Patients are often concerned about taking a larger dose of hormones, fearing a higher incidence of side effects, but they can be reassured because this larger dose, given in combination with EIAEDs, is comparable to that associated with normal doses. The failure rate of COC with AEDs is about twice that in the general population,[8] some of this is attributable to inadequate hormone dose, which is almost entirely preventable. If a women taking an EIAED and the larger dose of oestrogen is switched to a non-enzyme inducing AED, the higher dose of oestrogen should be maintained for a further two cycles.[9]

COCs may reduce the blood concentration of lamotrigine by 40%–60%,[10 11] so starting a COC in a patient already taking lamotrigine may result

Abbreviations: AED, antiepileptic drug; COC, combined oral contraceptive; EIAED, enzyme inducing antiepileptic drug; POP, progestogen only pill; MMR, major malformation rate; NTD, neural tube defect

in poorer control of the epilepsy, or may cause the recurrence of epilepsy in a patient whose epilepsy is under very good control; a small increment in the dose of lamotrigine is all that is required. There is no problem in giving lamotrigine to patients already taking a COC, because the dose of lamotrigine is titrated to the patients needs.

In summary, women taking EIAEDs should use COC containing at least 50 μg of oestrogen and tricycle with a four day pill free interval. Note that this is an unlicensed indication and such prescriptions are on a ''named patient basis''.

Combined contraceptive patches are also affected by EIAEDs and are not suitable for long term use by women taking these drugs.

The progestogen only preparations

The progestogen only pill (POP)

Progestogens are similarly affected by EIAEDs, aggravating other difficulties associated with this form of contraception, particularly breakthrough bleeding. Women taking EIEADs should take double the usual dose.[12]

The depot injection

This problem does not apply to the use of medroxyprogesterone acetate (Depo Provera, Pfizer), whose metabolism is proportional to hepatic blood flow, suggesting a virtually 100% clearance on first pass through the liver, so that enzyme induction has no additional effect and blood concentrations are not affected.[14]

The progestogen implant

EIAEDs do affect the three yearly progestogen implant that contains etonogestrel, (Implanon), so an additional daily progestogen pill is necessary,[15] which rather defeats the object.

In summary, women taking EIAEDs and a POP should consider a change of contraceptive method, otherwise use Cerazette and double the usual dose, but there is no need to change the dose of Depo-Provera or to shorten the interval between injections.

Post-coital contraception—''the morning after pill''

The efficacy of the morning after pill is also affected by EIAEDs. When using levonogestrel (Levonelle) the first dose should be doubled to two pills (1.5 mg) with a second dose at 12 hours of one pill (750 μg).[16]

Intra-uterine contraceptive devices

Coils that release hormones locally (the Mirena coil) are not affected by enzyme induction, and may be appropriate for some women taking EIAEDs.[17]

Post-partum contraception

COC preparations reduce the secretion of milk, but POPs may be used and should be started three weeks post-partum. If the mother is not breast feeding, a COC can be used from three weeks. Women taking EIAEDs should follow the protocols outlined above.

FERTILITY

Q: ''Could my drugs cause infertility?''
Q: ''Could my infertility be due to my drugs?''

Some AEDs may contribute to infertility in women, but women with epilepsy are less fertile than normal. A study of fertility ratios in women with epilepsy showed that the likelihood of pregnancy is considerably less than age matched controls, falling from 0.83 (0.54–1.21) in 15–19 year olds to 0.55 (0.14–1.39) at age 40–44.[18] This effect is likely to be multifactorial, including lowered libido, social and genetic factors, and not necessarily attributable to medication, although drugs may be a contributory factor. This also applies to sexual dysfunction, which is more common in women with temporal lobe epilepsy, especially if the epileptiform discharges are on the right.[19] Furthermore, it has been estimated that about 8% of menstrual cycles are anovulatory in normal subjects, but it may be as high as a third of all cycles in women with temporal lobe epilepsy,[20 21] particularly if they are taking valproate.[22]

Some AEDs have been associated with polycystic ovaries and the polycystic ovarian syndrome; valproate has been particularly implicated.[23 24] These findings have been disputed.[25 26] It may be that valproate induced obesity and the consequent increase in peripheral insulin resistance in patients with polycystic ovaries, together with a genetic susceptibility, are factors in the development of the polycystic ovarian syndrome; although polycystic ovaries and hyperandrogenism without hyperinsulinism have been found in some lean patients.[27] A consensus has been suggested for the investigation and management of these patients.[28]

TERATOGENICITY

Q: ''Will the drugs affect my baby?''

The incidence of all fetal abnormalities in the general population is between 2% and 3%. There maybe a small increased risk of fetal abnormalities in children of mothers with epilepsy who are not taking medication, but a recent meta-analysis[29] showed no increased risk and suggested that previous reports showed publication bias. However, there is definitely an increased risk from AEDs. An important adverse factor is the number of these drugs taken concurrently with an OR of 2.8 (1.1 to 9.7) for one drug, to 4.2 (1.1 to 5.1) for polytherapy.[30] Nakame *et al*[31] and Samren[32] found that the risk of major fetal abnormality rises from about double the natural risk with one AED to about six times the risk with four AEDs, but these patients would have less well controlled epilepsy and drug doses are likely to be comparatively high.

The fetal AED syndrome

This has been associated with several AEDs, particularly phenytoin (the fetal hydantoin syndrome) and valproate. The syndromes are not the same for each drug, although there are many similarities. Features of the fetal hydantoin syndrome[33] include microcephaly, hypertelorism, low set ears, short neck, transverse palmar creases, and minor skeletal abnormalities. This syndrome may be partly dose dependent and partly attributable to a genetically determined predisposition, which may explain why this condition can occur with quite low doses in some children and does not occur with quite high doses in others. Characteristic features of the valproate syndrome[34] are said to be arched eyebrows, short nose, thin upper lip, and broad nasal bridge. Other features include neural tube defects (NTDs), cleft lip and palate, radial ray defects, congenital heart defects, and genitourinary problems, again there is evidence of an hereditary susceptibility.[35] Major abnormalities asscociated with the barbiturates and hydantoins are congenital heart disease and cleft lip and palate; with valproate and carbamazepine are NTDs, hypospadias, and congenital heart disease. Phenytoin was once thought to be particularly implicated. However, a meta-analysis of the original data in five prospective European studies between 1971 and 1990, with a total of 1379 children and complete data from 1221 has shown an incidence of major defects with phenytoin monotherapy that is comparable to other AEDs (RR 2.2, 0.7 to 6.7).[36] Preliminary data from current prospective epilepsy and pregnancy registers are showing

similar data. It may be that the previously reported high risks were attributable to polytherapy and the lack of blood level control.

Data from the UK Epilepsy and Pregnancy Register on 3301 reports with 2637 outcomes have shown a major malformation rate (MMR) of 2.4% (0.9 to 6.0) in the 173 women with epilepsy who were not taking AEDs; it was 3.4% (2.7 to 4.4) in the 1891 patients on monotherapy and 6.5% (5.0 to 9.4) in the 573 patients on polytherapy. The monotherapy MMR for carbamazepine (700) was 2.3% (1.4 to 3.7) and for lamotrigine (390) 2.1% (1.0 to 4.0). For valproate (572) it was 5.9% (4.3 to 8.2), so that the MMR for valproate is significantly higher than the other most commonly used AEDs.[37] All pregnancies in women with epilepsy in the United Kingdom should be reported to the UK Epilepsy and Pregnancy Register as soon as the pregnancy is confirmed, so that accurate data about the effects of AEDs can become available, and this is particularly important for the recently introduced drugs*.

The use of valproate in women of childbearing age

The position of valproate in the treatment of these patients therefore needs special consideration. For women with certain types of epilepsy that respond best to valproate, particularly idiopathic generalised epilepsy with absence attacks, myoclonus, and photosensitivity, and who have achieved good control with this drug, the risk of recurrence of fits in pregnancy may need to be balanced against the increased risk of fetal abnormality.

The dose effect

In a re-analysis of five prospective studies,[36] valproate was associated with spina bifida in 3.8% of at risk pregnancies. An interesting feature of this series was that spina bifida did not occur with doses of less than a 1000 mg a day (0 of 54), 6.7% were found with doses of 1–1.5 g a day (2 of 30) and this was not significantly different from controls, and 37.5% if the dose exceeded 1.5 g a day (3 of 8). A retrospective study of 2000 pregnancies showed a relative risk (RR) of 1.0 if the dose of valproate was less than 600 mg a day, a RR of 2.2 with doses between 600 and 1000, and a RR of 3.9 (1.4 to 11.1) if the dose exceeded 1000 mg a day.[32] Mawer *et al*[38] and Kaneko *et al*[39] also found that major defects only occurred with doses above 1000 mg. Omtzigt *et al*[40] have reported that the average (SD) daily dose of valproate taken by the mothers of children with spina bifida was 1640 (136) mg compared with 941 (48) mg in those not affected; but all these studies involve too few patients to be sure that valproate, in doses even as low as 600 mg a day, is associated with a risk comparable to other AEDs.

Samren *et al*[36] showed some correlation with the size of each dose of valproate to the incidence of NTDs. This correlates with the findings in mice[41] that fetal abnormalities are as much associated with peak blood concentrations as the total daily dose. It may be that the protein binding becomes saturated, allowing free valproate to reach the developing fetal neural tube.

Valproate exposure and developmental delay

There is some evidence that children exposed to valproate in utero show an increased incidence of developmental delay.[42 43] Gaily *et al*[44] found no effect from in utero exposure to carbamazepine, but a significantly reduced verbal IQ (VIQ) in children exposed to polytherapy with valproate. An independent effect from valproate could not be determined because the results were confounded by low maternal education and polytherapy. Adab *et al*[45] showed that children exposed to valproate monotherapy had significantly lower VIQ scores when compared with children exposed to carbamazepine and to phenytoin monotherapy, and there was some evidence of a dose effect. Low VIQ was also associated with the occurrence of five or more tonic-clonic seizures during pregnancy and with low maternal IQ. There were higher rates of dysmorphic features in the valproate exposed children, and these were most common in those with low VIQ scores. Eriksson *et al*[46] found significantly lower full scale IQ in both mothers taking valproate and in their offspring, compared with those taking carbamazepine and women with epilepsy not taking any AEDs. These studies all entailed retrospective case ascertainment, though a few had prospective outcome measures. The numbers of children were small and the response rate low. A recent Cochrane review[47] concluded that the currently available data are insufficient to draw any definite conclusions, but the trends now emerging from the seven published studies are consistent. The confounding factors probably mean that these figures represent the worst outcome.

The use of valproate should therefore be avoided in women of childbearing age,[48] particularly in the obese, especially in obese adolescents, and in those women with menstrual irregularity. Consider withdrawal of valproate in women who develop obesity and or menstrual irregularity while on valproate.

Serious consideration should be given to changing drugs if at all possible for women of childbearing age who are established taking valproate, whether or not they are considering pregnancy, as about 50% of pregnancies in these women are unplanned.[49] If changing drugs is not appropriate, the risk may be reduced by spreading the dose throughout the day and to changing to Epilim Chrono to avoid peak blood concentrations. The total daily dose should be below 1 g a day and certainly below 1.5 g a day, so a suitable regimen might be Epilim Chrono 300 mg thrice daily. It is not appropriate to reduce the dose and add lamotrigine. The Glaxo-Smith-Kline register[50] of 360 patients taking lamotrigine monotherapy showed a MMR of 2.8% (1.5 to 5.2), and 3.1% (1.1 to 7.4) for lamotrigine in any polytherapy excluding valproate (163), but 10.5% (5.0 to 20.2) for lamotrigine with valproate (76).

In summary, it is advisable for all women with epilepsy taking AEDs and contemplating pregnancy to be taking a single drug and that drug should be given in the lowest possible dose. Of the old and well established drugs, carbamazepine has been thought to be the safest, and phenytoin monotherapy seems to be safer than was once thought. The risk of a major malformation is significantly greater with valproate than any of the other commonly used AEDs. Data are lacking about the risks of most of the newer AEDs, although animal experimental data and limited clinical reports suggest that they are no more teratogenic than the older AEDs, and perhaps safer. The UK pregnancy register shows no significant difference in risk of major abnormality for any of the commonly used AEDs, except for valproate; with this exception, parents can be reassured that there is a more than 90% chance that their infant will be entirely normal, and a 95% chance of not having a major malformation.

Folic acid

There is clear evidence that folic acid supplements reduce the risk of NTDs in the offspring of women at risk.[51 52] There is some evidence that folic acid supplements reduce the risk of NTDs in women taking EIAEDs.[53] Valproate and carbamazepine are known to be associated with an increased risk of NTDs, estimated at 1.5% and 0.5% respectively. Some AEDs

*The UK Epilepsy and Pregnancy Register: Department of Neurology (Ward 21), Royal Victoria Hospital, Belfast BT12 6BA, UK; http://www.epilepsyandpregnancy.co.uk

are folate antagonists, but Tomson *et al*[54] found no difference in red cell folate in pregnant women taking AEDs, mostly phenytoin and carbamazepine, compared with non-epileptic drug free pregnant women or with non-pregnant age matched healthy women. Furthermore, there was no correlation between red cell folate concentrations and doses or plasma concentrations of phenytoin or carbamazepine. Kirke *et al*[55] reported a significant association between NTDs and early pregnancy red cell folate concentrations, with a risk of 0.8 per 1000 births for those mothers with a red cell folate greater than 400 μg/l to 6.6 per 1000 for those with concentrations less than 150 μg/l; an eightfold difference and these authors estimated that 400 μg of folate a day would reduce the incidence of NTDs by 48%.

All women taking AEDs contemplating pregnancy should be given a folic acid supplement. This should anticipate pregnancy, as neural tube and cardiac defects occur in the first 28 days after conception. Neural tube closure takes place on about day 26, which is often before the woman realises she is pregnant. A folate supplement started after 30 days will have no protective effect against NTDs.

The correct advice is therefore to tell patients to start folic acid when they stop contraception. It has been suggested that all women potentially at risk should be given a folate supplement, because less than 50% of pregnancies in these patients are planned[48]; this is the basis for the fortification of food. Folic acid 5 mg once daily, which has no effect on epilepsy control, is widely recommended,[56] although there is no evidence that this dose is needed or even that it is effective in women taking AEDs. Doses of 360 μg and 400 μg were used and shown to be effective in two trials[57 58]; 800 μg in the Hungarian trial[52] and 4 mg in the MRC trial, chosen to avoid the possibility of a negative result from a lower dose[51]; but it is not known for certain whether less than 1 mg/day is sufficient for women taking AEDs and it has seemed better to give 5 mg a day to be safe. Lucock[59] has pointed out that more than 4–500 μg of pteroylmonoglutamate, the form of folate used in supplements, saturates the transformation during absorption to methylfolate, so that larger doses cannot be utilised, which suggests that there is no need to prescribe more than 1 mg a day. Even this dose will produce unmetabolised folic acid in the serum, the long term effects of which are unknown.[60] However, Wald *et al*[61] have constructed a model from published data linking the relation between serum folate and folate supplementation to the prevalence of NTDs according to maternal serum folate concentrations. This model predicts increasing protection from NTDs up to 5 mg/day, which remains the currently recommended dose.[62]

There is some animal experimental evidence[63] and a few case reports that suggest that folic acid may not protect against valproate induced NTDs,[64] which implies that valproate may act partly by a non-folate dependent mechanism.

INVESTIGATIONS DURING PREGNANCY

Q: ''Will I need any special tests?''

AED blood concentrations should be measured as soon as it is known that a woman is pregnant to establish a baseline; repeated as indicated for those drugs where blood concentraions are a useful guide to efficacy. Free drug concentrations, if available, provide more useful information.

All pregnant women taking AEDs, particularly valproate and carbamazepine, should have a series of high definition ultrasound scans. Anencephaly can be detected at 11 weeks, NTDs at about 16 to 18 weeks, congenital cardiac malformations at 18–20 weeks, and cleft lip and palate at about 20 weeks. Hypospadias and posterior cleft palates are not reliably detectable by ultrasound scanning. An increased maternal α fetoprotein concentration measured at 18 weeks may point to a NTD. Women should be advised about these procedures in advance of pregnancy.[65]

HYPEREMESIS

Q: ''What do I do about my drugs if I have morning sickness?''

Morning sickness occurs more commonly in the morning, but it may occur at any time throughout the day. Some AEDs (phenytoin, phenobarbitone) need only be taken once a day and can therefore be taken at night. Most drugs need to be taken twice a day, but the morning dose can be postponed by a few hours to avoid periods of sickness. If nausea and vomiting are severe, an antiemetic agent can be taken half an hour before the AED.

THE EFFECT OF FITS ON THE FETUS

Q: ''If I have a fit, will it harm my baby?''

Minor fits have no known affect on the fetus, but major convulsive seizures associated with cyanosis can produce anoxia in the infant. There is some evidence that seizures in early pregnancy are associated with an increase in major malformations.[66] In late pregnancy, if a fit results in a fall, injury to the fetus may occur and could precipitate early labour or miscarriage.

It is very important to maintain AED administration in pregnancy because both fits and drugs can affect outcome. Furthermore, sudden withdrawal may precipitate status epilepticus, with serious consequences for both mother and child.

THE EFFECT OF PREGNANCY ON FITS

Q: ''Will my fits get worse during pregnancy?''

Pregnancy does not usually have much effect on the control of epilepsy, a survey in 1994[67] showed that about a fifth of patients have increased fits, more than a half remain unaffected, and about a quarter have fewer fits, and this does not change significantly during the three trimesters. Fits are more likely to increase in women with poorly controlled epilepsy and women with increased seizures in pregnancy are often found to have subtherapeutic blood concentrations.[68] Poor compliance may be a factor, requiring discussion and advice. Otherwise it may be necessary to increase the dose during pregnancy, monitoring the AED blood concentration; although it is not usually necessary to do so in well controlled patients.

Although AED concentrations tend to fall during pregnancy, this may be partially offset by a rise in the proportion of the free drug because of changes in protein binding. This is particularly so for those drugs that are highly protein bound, such as phenytoin, valproate, and carbamazepine. Pregnancy has a greater effect on AEDs that are metabolised in the liver compared with those that are mostly cleared by renal excretion (table 1).

If the dose is changed during pregnancy it is likely to need adjustment after delivery. Lamotrigine poses a particular problem in this respect with a pronounced increase in clearance rate during pregnancy. Tran *et al*[69] found this to be >65% between preconception and delivery, so that 11 of 12 women required an increase in dose. Pennell *et al*,[70] in nine women, found a mean (SD) change from baseline in

Table 1 Protein binding and clearance of AEDs

	% Protein binding	Clearance
Tiagabine	96	liver
Phenytoin	90	liver
Valproate	90	liver
Clonazepam	86	liver
Carbamazepine	75	liver
Lamotrigine	55	liver
Phenobarbitone	45	liver/renal
Oxcarbazepine	40	liver
Topiramate	15	liver
Levetiracetam	10	renal
Gabapentin	0	renal
Vigabatrin	0	renal
Pregabalin	0	renal

apparent clearance of 92 (110)% in the first trimester, 121 (138)% in the second, and 315 (214)% in the third trimester, overall 164%, but with very wide individual variation. de Haan *et al* found a gradual decline in lamotrigine level to dose ratio to 40% with a seizure increase in 9 of 12 pregnancies.[70a] As this effect starts early in pregnancy, the dose escalation needs to be started after the first month,[70 71] and may need to be more than doubled by the third trimester.[71] After delivery, Berry[72] found rises of 200%–300% within a few weeks. Ohman *et al*[73] found a median increase of 170% (0 to 630), so it is important to reduce the dose in the postpartum period.

Patients with poorly controlled epilepsy should be warned that an increase in dose may be necessary during pregnancy; those with good control can be advised that any change in their drug is unlikely to be necessary, except for women taking lamotrigine.

MANAGEMENT OF A FIRST FIT IN PREGNANCY

Excluding eclampsia, it is unusual for a first fit to occur during pregnancy without obvious cause. These patients should be investigated because there is a higher incidence of underlying structural lesions; for example, meningiomas and arteriovenous malformations may present in pregnancy because of swelling of the lesion. Other causes include thrombosis, both arterial and venous, and subarachnoid haemorrhage. Patients with toxaemia may present with epilepsy and if this is the cause of fits around the time of delivery, including the immediate postpartum period, epilepsy is unlikely to be an ongoing problem.

PSEUDOSEIZURES

It has been estimated that between 10% and 45% of apparently intractable epilepsy is attributable to pseudoseizures[74] and most of these patients are young women. Perhaps 20% of patients with confirmed pseudoseizures also have epilepsy.[75] These patients can be very difficult to identify and often go misdiagnosed for many years. The clinical features include prolonged fits while awake, pelvic thrusting, eye closure with resistance, lack of postictal confusion or drowsiness, and normal investigations. The diagnosis is made by recording a normal EEG during a seizure, which may require telemetry, and the finding of a normal prolactin level after a fit. These patients are notoriously difficult to treat and should be referred to a specialist centre.

EPILEPSY DURING DELIVERY

Q: ''Will there be any problems at birth?''

(This question has been identified as a major and often unexpressed concern.)

Effect on the mother

There is no increased risk of purely obstetric problems in women with epilepsy,[76] but all pregnant women with epilepsy taking AEDs should have their babies delivered in hospital. The increased risk of epilepsy at delivery and in the next 24 hours, said to be about 3% of women at risk,[1] is usually attributable to failure to take AEDs, lack of sleep, or impaired drug absorption. Patients with generalised epilepsy are more likely to have seizures during delivery than patients with partial epilepsy,[77] particularly if the AED concentrations are barely or sub-therapeutic.[62] The risk of status epilepticus is very small, but carries a high mortality risk for both mother and infant. In 29 such patients identified in the literature,[78] there was a 50% fetal mortality (14 of 29) and nine maternal deaths. Clobazam may be used prophylactically in women thought to be at particular risk.

Effect on the infant

Some AEDs, particularly primidone, phenobarbitone, and the benzodiazepines, are sedating and some infants show withdrawal symptoms from these drugs in the first few days of life. Withdrawal fits are rare, but are said to be most common with phenobarbitone.

VITAMIN K

The EIAEDs cause a reduction in vitamin K dependent clotting factors by an effect on the synthesis of factors 2, 7, 9, 10 and protein C and S. Although giving vitamin K to women in the last few weeks of pregnancy does raise the fetal plasma vitamin K1 concentration appreciably, it remains an order of magnitude lower than maternal levels because of poor placental passage and low concentrations of transport lipoproteins in fetal plasma; so that fetal plasma vitamin K concentrations are very low in new born babies.[79] The vitamin K concentrations rises to near normal in about a week in breast fed babies and reaches eight times the normal value in babies fed with vitamin K fortified formula milk.

The risk of bleeding can be divided into three groups.[80] (1) The early onset bleeds, which occur in the first 24 hours and are nearly always attributable to drugs, including AEDs; (2) the classic neonatal bleeding, which occurs in the first week; and (3) the late incidence of bleeding between one week and three months, with a peak at two to six weeks. Intracerebral haemorrhage is rare in the first week after the first 24 hours, but occurs in 50% of patients with late bleeding.[81] Intramuscular vitamin K given at birth seems to be almost completely effective in preventing bleeding.[82] Further vitamin K should be given to babies who are exclusively breast fed for more than one month.

Giving intramuscular vitamin K1 at birth was a standard practice until the report in 1992 of an increase in childhood cancers in babies given intramuscular vitamin K, but not in babies given oral vitamin K or no vitamin K.[83] There is now an extensive literature on this topic; it seems clear that there is no increased risk of solid tumours, but a small increased risk of acute lymphoblastic leukaemia cannot be absolutely excluded on the available data.[84–87] Folate supplements may reduce the risk of acute lymphoblastic leukaemia.[88]

The theoretical risk of bleeding in children born of mothers taking EIAEDs is sufficient for all pregnant women taking these drugs to take oral phytomenadione (vitamin K1) 20 mg daily for at least one month before delivery to reduce the risk of bleeding in the first 24 hours, and vitamin K1 0.5 mg should be given intramuscularly immediately after delivery. Although Kaaja *et al*[89] found no increase in the incidence of bleeding in 662 infants of mothers taking EIAEDs, compared with 1324 controls, the numbers may have been insufficient to show an effect.

BREAST FEEDING

Q: ''Will I be able to breast feed?''

All the AEDs are excreted in breast milk, but for most only in low concentrations, so there is no reason why mothers taking AEDs should not breast feed, although with caution for phenobarbitone and primidone. The amount of drug received by the infant is very considerably less than the fetus receives during pregnancy. For example, calculations of the largest amount of drug likely to be received daily by a fully breast fed baby expressed as a percentage of the lowest recommended daily therapeutic dose for an infant, give the following figures: carbamazepine <5%, phenytoin <5%, valproate <3% and phenobarbitone >50%; so that phenobarbitone and primidone may cause drowsiness. Fetal hepatic immaturity results in a considerable increase in the blood half life of phenobarbitone. In adults the half life is around 100 hours (75–125), but in the newborn baby it may be more than 200 hours.[90]

There is little or no information about the newer drugs, except lamotrigine, which is excreted in high levels in breast milk (40%–80% of maternal concentrations),[72] and when combined with slow fetal clearance because of hepatic immaturity, infant blood concentrations may reach 60% (range 47–77) of the maternal blood concentration,[72] a problem that is compounded if lamotrigine is given with valproate. Topiramate and levetiracetam also reach high concentrations in breast milk, but this does not seem to produce significant values in breast fed babies.[91 92]

Breast feeding should be encouraged in women with epilepsy taking all AEDs. New drugs should not be introduced in the postpartum period to women who are breast feeding or only with great caution; this particularly applies to phenobarbitone, primidone, and lamotrigine. If AED treatment seems to be causing drowsiness in the infant, it may still be possible to breast feed, alternating with bottle feeding.

POSTPARTUM MATERNAL EPILEPSY

Q: ''What happens if I have a fit when I am by myself with the baby at home?''

Mothers with uncontrolled major epilepsy should not be left alone with small children. Maternal epilepsy probably presents a greater risk to infants and toddlers than to the fetus. The child could be injured if held by the mother at the start of a fit or if left unattended during the mother's fit. Mothers should be warned of this risk and seek advice about appropriate precautions, for example, changing nappies on the floor and only bathing infants when somebody else is present. Mothers with juvenile myoclonic epilepsy may be at particular risk when woken early by their infant.[93]

If the dose of AED was increased during pregnancy, it is likely to need adjustment in the postpartum period, this applies particularly to lamotrigine.[68–70 72 73]

HEREDITARY RISKS

Q: ''Will my baby have epilepsy?''

A child inherits its epileptic liability from both parents. The risk depends on the type of epilepsy. There is no significant risk if the mother has partial epilepsy from an acquired lesion. The overall risk of a child of a parent with idiopathic generalised epilepsy having epilepsy before the age of 20, excluding febrile convulsions, is about 4%, compared with 0.5% in the general population. If there is already one sibling who developed epilepsy before the age of 10, the risk rises to about 6%, if one parent and a sibling are affected the risk is about 10%, and if both parents or one parent and a first degree relative of the other parent have epilepsy, the risk is about 15%.[94] These figures exclude the genetically determined epilepsy syndromes, such as juvenile myoclonic epilepsy and those inherited conditions that may be associated with epilepsy, such as tuberose sclerosis and neurofibromatosis.[95]

If there is a family history of a known inherited epilepsy syndrome or of a condition that has a strong association with epilepsy, the risk is that of the syndrome. Patients should be referred for specialist genetic advice.

COUNSELLING

Women with epilepsy who are contemplating pregnancy should have the diagnosis re-evaluated and if necessary re-investigated. It has been estimated that about 5%–10% of these patients do not have epilepsy[93 96] and 7% are found to have a structural lesion.[93] Many are taking unsuitable drugs and often at inappropriate doses. Reconsideration of the diagnosis may permit withdrawal of AEDs. In some circumstances an endocrinology screen may be appropriate.

It is very important that all patients with epilepsy are fully informed about these issues, but not necessarily all at the same time and at the same age. It would be appropriate for paediatricians as well as neurologists and general practitioners, who often look after patients with epilepsy up to the age of 15 or 16, to mention some of these issues and in particular contraception and folic acid. Teratogenicity, ultrasound scanning, and breast feeding should be discussed with women who are contemplating pregnancy and they should be given the opportunity to discuss any other matters they wish to raise. Women can be reassured that there is a more than 90% chance of having a normal baby. Poor communication is a common problem; many patients may not understand the concept of percentage risk. It may help to explain that 5% risk or a 1 in 20 chance of an abnormal event is a 95% chance of normality. Positively framed information changes the perception of teratogenic risk in pregnant women.[97]

CATAMENIAL EPILEPSY

Many women report that their episodes occur in relation to their menstrual periods, but there is a problem with definition.[98] If it is to influence management, it is necessary to take a very narrow view and restrict the term to the time from a day before the onset of a period to the first two days of a period. The cycle must also be very regular, so that the next period can be forecasted accurately; otherwise there are no treatment implications. The precise reason for catamenial epilepsy is unknown, but may be related to the fact that oestrogen is softly epileptogenic, whereas progesterone is weakly antiepileptogenic.[99] The rapid reduction in serum progesterone concentrations just before a period may make women more susceptible to epilepsy at that time. Changes in fluid balance may also play a part, but giving diuretics starting a week before a period is due is not effective.

It is sometimes appropriate to treat catamenial epilepsy with intermittent treatment in addition to regular drug treament. However, the patient must show diary evidence that the episodes are confined to a few days around the onset of a period and that the periods occur at very regular intervals, so that day one of the next period can be accurately predicted. It may then be reasonable to give an additional AED starting a few days before a period is due. For practical purposes this needs to be a quick acting drug that can be given at full dose in addition to the ongoing

drug—clobazam[100] is most widely used, clonazepam or acetazolamide are alternatives.

Intermittent treatment without any background AED is not usually effective, because the fits are often displaced until after the intermittent treatment stops. Hormonal manipulation is usually ineffective and gynaecological procedures are contraindicated.

THE MENOPAUSE AND BONE DENSITY

The menopause tends to occur earlier in women with epilepsy and there is a negative correlation between the age at the menopause and estimated lifetime seizures. For women with a high seizure frequency this is about three to four years.[101] There is often an increase in seizure frequency at the menopause and about a one third reduction in postmenopausal women, particularly in women who had catamenial epilepsy.[102] Hormone replacement therapy may be used if clinically indicated; there is some clinical evidence to support the theoretical risk of an increase in fits attributable to oestrogen.[2]

AED use is an independent predictor of increased risk of fractures.[103] This increased risk comes from the effect of EIAEDs on vitamin D, added to the natural risk of osteoporosis because of age and postmenopausal status, as well as the increased risk not only from seizures, but also from unsteadiness because of some AEDs.[104] These women should have a bone health screen and be advised accordingly.[105]

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