Anticonvulsant medication

Antiepileptic drug therapy during pregnancy: the neurologist's perspective

S Shorvon

Antiepileptic medication in pregnancy

Epilepsy causes disadvantage for many reasons, and for women there are particular problems associated with epilepsy in pregnancy. Some are the direct result of seizures, some result from the drug treatment, and some are secondary handicaps because of stigmatisation. It was not very many generations ago that women with epilepsy were routinely advised not to reproduce, and in many countries, even in recent times, there have been legal interdictions on marriage and childbearing. In the western democracies, less prejudicial attitudes now prevail, but recent epidemiological evidence still shows that women with epilepsy, when compared to controls, have lower fertility rates,[1] children born later, lower rates of marriage,[2] higher rates of sexual dysfunction,[3] and hormonal changes.[4] There are currently about 75 000 women of childbearing age on treatment for epilepsy in the UK,[1] and about 0.3-0.4% of all births are to mothers with epilepsy. The neurologist has a duty to provide information and advice on many issues relating to the management of epilepsy in pregnancy, an increasing imperative as these issues have become the focus of much public interest. A key to all decision making is that the women should be fully involved and informed about the choices, and decisions made after full discussion.

Ideally the issues relating to epilepsy and pregnancy should be brought up well in advance of any planned pregnancy to allow informed and well considered choices. In preconceptional counselling, it is first necessary to decide whether treatment is indicated at all. This will depend on an assessment of the balance of risks of drug treatment versus those of the untreated epilepsy. A decision to withhold treatment might be made, for instance in some patients with minor seizures, reflex seizures, seizures at night, or infrequent seizures. Rules are not possible to formulate and decisions are highly individual.

The risk to the fetus of the antiepileptic drugs (the risk of teratogenicity) is of course a major concern, but understanding of this topic is evolving and this complicates the advice that can be given. The first conclusive report of anticonvulsant teratogenicity was a letter in *The Lancet* by Meadow,[5] who reported hare lip and cleft palate and other abnormalities in six children whose mothers were taking phenytoin, barbiturate, and troxidone. Before this, there were no concerns about prescribing in epilepsy during pregnancy, and it is worth noting that phenobarbitone had been in use since 1912, phenytoin since 1938, and troxidone (a severe teratogen) since 1946. Other reports followed, and by the mid 1970s it was believed that the risk of fetal malformation in the infants of mothers taking antiepileptics was about twice that expected.[6 7] Nevertheless, the orthodox advice was still generally that mothers should continue therapy (with folate supplementation) in view of the greater perceived risk of uncontrolled epilepsy. In 1975, the fetal hydantoin syndrome was first reported.[8] At that time, the main prescribed antiepileptics were phenytoin, phenobarbitone, carbamazepine, and valproate, and the latter two drugs were increasingly recommended as first line drugs of choice in pregnancy. In 1981, valproate induced spina bifida was first reported, a risk estimated now to be about 1-2%,[9] and during the 1980s reports accumulated of this and other major malformations resulting from valproate. An editorial in the *BMJ* in 1985, however, still placed valproate as the drug of choice for grand mal epilepsy in young women. A fetal valproate syndrome was first suggested in 1987, although its features and indeed its existence are still controversial. Spina bifida was noted to be associated with carbamazepine in 1990 (now thought to have a frequency of about 0.5-1% of exposed pregnancies), but during the 1990s most opinion concurred that this was the safest of the conventional drugs. Large studies were carried out in the 1990s, and a review in 1995 ranked the drugs for teratogenetic risk (in decreasing order: primidone, valproate, phenytoin, carbamazepine, and phenobarbitone). In recent studies, major malformations have been reported in between 6-9% of newborns exposed to maternal antiepileptics, a two- to threefold greater risk than in unexposed children.[11–14] Specific patterns occur, with valproate exposure associated with neural tube and skeletal defects, carbamazepine with neural tube and congenital heart defects, and phenytoin with congenital heart and digital defects and orofacial clefts.[15] A range of newer drugs has been introduced to treat epilepsy in the last 10-15 years (including vigabatrin, lamotrigine, topiramate, tiagabine, and levetiracetam), but experience in pregnancy, even after 10 or more years of prescribing for some of these drugs, is slight and their teratogenetic potential is unclear. Some have proven teratogenicity in animals, and in view of the delay in recognition of the teratogenicity of previous drugs, there is a general, but not universal, reluctance to expose pregnant women to an essentially unknown risk.

The research emphasis until quite recently has been on the potential for antiepileptic drugs to cause major morphological anomalies. Growth retardation and minor morphological changes (for example, those comprising the so-called fetal syndromes of phenytoin, valproate, barbiturate, or benzodiazepines) are more controversial, and studies are confounded by genetic as well as other congenital factors, leading some to suggest that the various minor changes are in fact often not the result of medication.[16] In the past few years, evidence has also been gathered suggesting that the antiepileptic drugs given in utero may result in intellectual disability and behavioural change in the offspring in later life.[17–19] This is a worrying spectre, but conclusive proof is lacking to date. The article by Dean *et al* on page 251 of this issue adds to the concerns. Studies are of course difficult, and gold standard blinded and prospective investigations will take years to perform. If antiepileptic drugs, taken during pregnancy, do have a downstream effect on learning and behaviour, which is only manifest years after birth, the risk/benefit ratio of taking/not taking drugs during pregnancy will be altered. The frequency and severity of these effects is still essentially unknown, and predictive factors have not been identified. This makes neurological advice very difficult to give. The situation is complicated by the activities of some pharmaceutical companies, who since the mid 1990s, have been actively marketing drugs on the basis of their presumed safety or otherwise in pregnancy, making claims which have obscured rather than clarified rational decision making.

What advice about teratogenicity should be given to the women contemplating pregnancy now? The known risks of the major malformations should be discussed, and the potentially greater

risks of relatively minor morphological changes. The possibility of later intellectual or behavioural difficulties should be raised, but it should be emphasised that currently the risk is unquantifiable. Some epilepsies are the result of genetic and heritable factors which may also be associated with intellectual delay, and the differentiation of drug versus genetic parental influences can be very difficult. Any counselling about risks of neurological defects in the offspring require an understanding of the maternal epilepsy syndrome. As the risk of teratogenicity is greatest with exposure in the first trimester (the time of greatest sensitivity is 3-4 weeks for neural tube defects, 4-8 weeks for congenital heart defects, and 6-10 weeks for orofacial clefts) and the risk of seizure related fetal injury greatest in the last trimester, one strategy is to initially withhold treatment and to start therapy in the second or third trimester. This course of action requires counselling and experience. If a women presents for advice regarding therapy having discovered that she is already pregnant, the drug influences causing major malformation may well have already applied. Altering therapy will therefore not reduce these risks. More subtle effects (for example, growth retardation, minor anomalies, cognitive effects), though, may develop later, and, again in spite of any conclusive evidence, it thus seems reasonable to reduce therapy where possible.

The women must weigh up the risks of drug therapy against those of seizure induced morbidity and mortality, both to her and the unborn fetus. Maternal morbidity includes the physical risks of accidents and the many psychosocial consequences of active epilepsy. Fetal morbidity in epilepsy is largely related to the mechanical risks of falling and of convulsions during the later stages of pregnancy, to the risks of seizures occurring during delivery, and to status epilepticus. Convulsions during delivery are a particular problem. These have resulted in maternal death and also in fetal asphyxia.[20] One to two percent of women with epilepsy will have a convulsion during delivery,[21 22] a risk presumably lowered by therapy. A case report of complex partial seizures during labour showed significant fetal heart rate decelerations and prolonged uterine contractions,[23] and most seizures will also impair the mother's ability to cooperate during the delivery. These facts no doubt contribute to the greatly increased rate of caesarian section among epileptic women. Prolonged seizures, and in particularly status epilepticus, carry an undisputed risk. Teramo and Hiilesmaa,[24] for instance, reported fetal death in about 50% of cases with status epilepticus during pregnancy and in 30% of the mothers. There is also some experimental evidence that seizures during pregnancy can have deleterious effects on the fetus, perhaps because of exposure to the short duration episodes of hypoxaemia or lactic acidosis which accompany severe seizures, although significant damage induced in this manner seems intuitively unlikely. Prospective studies have not shown an increased risk of birth defects in mothers who have seizures during pregnancy, although there are case reports of cognitive dysfunction in the offspring of women who have had convulsive as well as non-convulsive seizures during pregnancy.[17] Currently, most women with epilepsy are treated with antiepileptic drugs and the decision not to do so needs to be taken by a neurologist experienced in this area, and after full and frank discussion of the risks with the patient.

There are other points which should be part of the neurological management of epilepsy in pregnancy and pre-pregnancy counselling. Primary among these is the prescription of folic acid. Folate has been clearly shown to reduce the frequency of neural tube defects in the normal population.[25 26] As some antiepileptic drugs (for example, phenytoin, phenobarbitone, and carbamazepine) reduce folate levels, and as neural tube defects are increased by therapy with some drugs (for example, valproate and carbamazepine), it seems sensible to ensure folate is taken by pregnant women with epilepsy, although it has to be admitted that few studies have been carried out to show beneficial effects in epilepsy. Folate should be given at higher doses (4 mg/day is often recommended) than in non-medicated women owing to the diminished absorption and increased metabolism of folate in patients on hepatic enzyme inducing antiepileptic drugs. Second is the question of monitoring and investigation. High quality ultrasound at 16-20 weeks of gestation has a high sensitivity and specificity in detection of major malformations, including more than 90% of neural tube defects, and a high proportion of cardiac malformations, skeletal defects, and orofacial clefts. If therapeutic termination is acceptable, this reduces very considerably the risks of offspring with malformations. Ultrasound at week 33-34 can also be useful in showing intrauterine growth retardation. Amniocenteses for amniotic fluid alpha-fetoprotein can be considered, but carries a 0.5-1.0% risk of precipitating abortion. Tailoring antiepileptic drug therapy can also be important. Where possible, single drug therapy should be used, as the risks of teratogenicity are clearly shown to be greater in polytherapy. It has widely been recognised since the 1980s that the more drugs that are used in combination, the greater are the risks. The dose of the chosen drug(s) should be minimised, as there is a clear relationship between dose of some drugs (for example, valproate) and teratogenic effect. The total dose of valproate (and possibly other drugs) should be divided and given three or four times a day to minimise high peak concentrations of the parent drug or its metabolites. The pharmacokinetics of most antiepileptic drugs change in pregnancy, and levels of phenytoin, phenobarbitone, and carbamazepine tend to fall, especially in later pregnancy.[22 27 28] The ratio of free/total serum levels of phenytoin alter in pregnancy and measurement of free levels is in some circumstances more reliable than that of total levels. Maternal ingestion of enzyme inducing antiepileptic drugs can result in low fetal vitamin K levels, and a consequential risk of perinatal haemorrhage owing to induced deficiencies of factors II, VII, IX, and X. Widely given advice, therefore, is to give oral vitamin K_1 at a dose of 10-20 mg/day to the mother in the last month of pregnancy and also 1 mg intramuscularly to the infant at birth.[29 30] Counselling of the pregnant women (and the women contemplating pregnancy) should also include advice on the risk of epilepsy in the offspring, the increased risks of complications during pregnancy,[31–33] the advisability of breast feeding,[34–36] and precautions to be taken if maternal seizures are likely in relation to the care of the newborn. The commonest complaint of patients with epilepsy about hospital outpatient services, in the UK and elsewhere, is a perceived lack of information.[39] This has been found to be particularly true for advice about pregnancy in epilepsy, and there is no area in epilepsy practice in which counselling and discussion are more important.

J Med Genet 2002;**39**:248–250

Author's affiliations
S Shorvon, Department of Clinical Neurology, Institute of Neurology, University College London, and National Neuroscience Institute, Singapore

Correspondence to: Professor S Shorvon, Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK; sshorvon@singnet.com.sg

REFERENCES

1 **Wallace H**, Shorvon SD, Tallis R. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age specific fertility rates of women with epilepsy. *Lancet* 1998;**352**:1970-4.
2 **Callaghan N**, Crowley M, Goggin T. Epilepsy and employment, marital, education and social status. *Irish Med J* 1992;**85**:17-19.
3 **Demerdash A**, Shaalan M, Midani A, Kamel F, Bahri M. Sexual behaviour of a sample of females with epilepsy. *Epilepsia* 1991;**32**:82-5.
4 **Duncan S**. Polycystic ovarian syndrome in women with epilepsy: a review. *Epilepsia* 2001;**42**(suppl 3):60-5.

5 **Meadow SR**. Anticonvulsant drugs and congenital abnormalities. *Lancet* 1968;**ii**:1296.
6 **Speidel BD**, Meadow SR. Maternal epilepsy and abnormalities of the fetus and newborn. *Lancet* 1972;**ii**:1196-7.
7 **Smithells RW**. Teratogenic effects of anticonvulsants. *Br Med Bull* 1976;**32**:27-33.
8 **Hanson JW**, Smith DW. The fetal hydantoin syndrome. *J Pediatr* 1975;**87**:285-90.
9 **Omtzigt JGC**, Los FJ, Grobbee DE, Pijpers L, Jahoda MGJ, Brandenburg H, Stewart PA, Gaillard HLJ, Sachs ES, Wladimiroff JW, Lindhout D. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology* 1992;**42**(suppl 5):119-25.
10 **Rosa FW**. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991;**324**:674-7.
11 **Samrén B**, van Duijn C, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, Mannagetta GB, Deichl AW, Gaily F, Granstrom ML, Meinard H, Grobbee DE, Hofman A, Janz D, Lindhout D. Maternal use of antiepileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia* 1997;**38**:981-90.
12 **Samrén B**, van Duijn C, Christiaens GC, Hofman A, Lindhout D. Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Ann Neurol* 1999;**46**:739-46.
13 **Canger R**, Battino D, Canevini MP, Fumarola C, Guidolin L, Vignoli A, Manoli D, Palmieri C, Molteni F, Granata T, Hassibi P, Zamperini F, Pardi G, Avenzini G. Malformations in offspring of women with epilepsy: a prospective study. *Epilepsia* 1999;**40**:1231-6.
14 **Kaneko S**, Battino D, Andermann E, Wada K, Kan R, Takeda A, Nakane Y, Ogawa Y, Avanzini G, Fumarola C, Granata T, Molteni F, Pardi G, Minotti L, Canger R, Dansky L, Oguni M, Lopes-Cendes I, Sherwin A, Andermann F, Jeni MH, Okada M, Teranishi T. Congenital malformations due to antiepileptic drugs. *Epilepsy Res* 1999;**33**:145-58.
15 **Holmes LB**, Harvey EA, Coull BA, Huntington K, Khoshbin S, Hay A, Ryan L. The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001;**344**:1132-8.
16 **Gaily E**. Minor anomalies and effects on psychomotor development associated with maternal use of antiepileptic drugs. In: Tomson T, Gram L, Sillanpää M, Johannessen SI, eds. *Epilepsy and pregnancy*. Petersfield: Wrightson Biomedical Publishing Ltd, 1997:63-70.
17 **Gaily E**, Kantola-Sorsa E, Granström ML. Specific cognitive dysfunction in children with epileptic mothers. *Dev Med Child Neurol* 1990;**32**:403-14.
18 **Reinisch JM**, Sanders SA, Mortensen EL, Rubin DB. In utero exposure to phenobarbital and intelligence deficits in adult men. *JAMA* 1995;**274**:1518-25.
19 **Adab N**, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2001;**70**:15-21.
20 **Teramo K**, Hiilesmaa V, Bardy A, Saarikoski S. Fetal heart rate during a maternal grand mal epileptic seizure. *J Perinat Med* 1979;**7**:3-6.
21 **Bardy AH**. Incidence of seizures during pregnancy, labor and puerperium in epileptic women: a prospective study. *Acta Neurol Scand* 1987;**75**:356-60.
22 **Tomson T**, Lindbom U, Ekqvist B, Sundqvist A. Epilepsy and pregnancy: a prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. *Epilepsia* 1994;**35**:122-30.
23 **Nei M**, Daly S, Liporace J. A maternal complex partial seizure in labor can affect fetal heart rate. *Neurology* 1998;**51**:904-6.
24 **Teramo K**, Hiilesmaa VK. Pregnancy and fetal complications in epileptic pregnancies. In: Janz D, Dam M, Richens A, Bossi L, Helge H, Schmidt D, eds. *Epilepsy, pregnancy and the child*. New York: Raven Press, 1982:53-9.
25 **MRC Vitamin Study Research Group**. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;**338**:131-7.
26 **Czeizel AE**, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;**327**:1832-5.
27 **Perucca E**. Drug metabolism in pregnancy, infancy and childhood. *Pharmacol Ther* 1987;**34**:129-43.
28 **Yerby MS**. Friel PN. McCormick K. Antiepileptic drug disposition during pregnancy. *Neurology* 1992;**42**(suppl 5):12-16.
29 **Cornelissen M**, Steegers-Theunissen R, Kollee L, Eskes T, Motohara K, Monnens L. Supplementation of vitamin K in pregnant women receiving anticonvulsant therapy prevents neonatal vitamin K deficiency. *Am J Obstet Gynecol* 1993;**168**:884-8.
30 **Hey E**. Effect of maternal anticonvulsant treatment on neonatal blood coagulation. *Arch Dis Child* 1999;**81**:F208-10.
31 **Hiilesmaa VK**, Bardy A, Teramo K. Obstetric outcome in women with epilepsy. *Am J Obstet Gynecol* 1985;**152**:499-504.
32 **Yerby M**, Koepsell T, Daling J. Pregnancy complications and outcomes in a cohort of women with epilepsy. *Epilepsia* 1985;**26**:631-5.
33 **Sabers A**. Complications during pregnancy and delivery. In: Tomson T, Gram L, Sillanpää M, Johannessen SI, eds. *Epilepsy and pregnancy*. Petersfield: Wrightson Biomedical Publishing Ltd, 1997:105-111.
34 **Vinge E**. Breast-feeding and antiepileptic drugs. In: Tomson T, Gram L, Sillanpää M, Johannessen SI, eds. *Epilepsy and pregnancy*. Petersfield: Wrightson Biomedical Publishing Ltd, 1997:93-103.
35 **Morrell MJ**. Guidelines for the care of women with epilepsy. *Neurology* 1998;**51**(suppl 4):S21-7.
36 **Hägg S**, Spigset O. Anticonvulsant use during lactation. *Drug Safety* 2000;**22**:425-40.
37 **Poole K**, Moran N, Bell GJ, Solomon JK, Kendall S, McCarthy M, McCormick D, Nashef L, Johnson AJ, Sander JW, Shorvon SD. Patients' perspectives on services for epilepsy: a survey of patient satisfaction, preferences and information provision in 2394 people with epilepsy. *Seizure* 2000;**9**:551-8.