Should valproate be taken during pregnancy?

Mervyn J Eadie[1]
Frank JE Vajda[2]

[1]Department of Medicine, University of Queensland, Royal Brisbane Hospital, Brisbane, QLD, Australia; [2]Australian Centre for Clinical Neuropharmacology, Raoul Wallenberg Centre, Neurosciences and University of Melbourne at St Vincent's Hospital, Melbourne, VIC, Australia

Abstract: The Australian Registry of Antiepileptic Drug Use in Pregnancy includes 172 instances in which women took sodium valproate, with or without other antiepileptic drugs, during pregnancy. These pregnancies resulted in a substantially higher ($p < 0.05$) rate of malformed offspring (15.1%) compared with 348 pregnant women who took antiepileptic drugs other than valproate (2.3%) and 40 pregnancies in epileptic women who took no antiepileptic drugs (2.5%). At valproate doses of 1400 mg and below per day, the mean rate of pregnancies with fetal malformations was 6.42% and did not seem to be dose-dependent. At higher valproate doses, the mean rate of pregnancy with fetal malformation was 33.9% and appeared to increase with increasing drug dosage. This finding suggests the need for reappraisal of the use of valproate in women who may become pregnant or are pregnant whilst the drug is taken. The therapeutic policy adopted may depend on whether valproate doses below 1400 mg per day are regarded as safe for the fetus. This study indicates that the risk of malformation associated with such doses was just statistically significantly ($p < 0.05$) higher than that associated with other antiepileptic drugs. Various possible clinical scenarios are discussed.
Keywords: epilepsy, malformations, pregnancy, valproate

Introduction

For over at least a third of a century, since the report of Meadow (1970) and other early work reviewed by Janz (1976), the medical profession has been aware that the intake of antiepileptic drugs (AEDs) in pregnancy is associated with an increased risk of malformation in the offspring. This association has been confirmed repeatedly in subsequent studies (Hart 2003). No specific patterns of malformation seem to have been associated with any individual antiepileptic drug, although several reports have suggested a particular association between valproate intake in pregnancy and the occurrence of neural tube defects (Anon 1982; Nau and Hendrickx 1987; Omtzigt et al 1992). Although the risk of malformations is now well documented for the longer established AEDs, less information is available regarding the AEDs introduced into therapeutics in the past decade. To address this, an Australian Pregnancy Registry was set up in 1998 to recruit women nationwide on a volunteer basis. It recorded the outcomes of pregnancy in those taking AEDs and also in women with untreated epilepsy (Vajda et al 2003). The data in this Registry have been reviewed periodically. Sufficient information on the outcome of pregnancies in which valproate has been taken is now available. An assessment of these data and some of the questions it raises are considered below.

Materials and methods

The Australian Registry of Antiepileptic Drug Use in Pregnancy depends on the voluntary notification of women who take AEDs during pregnancy, those who are suffering from epilepsy but do not take AEDs whilst pregnant, and those who take AEDs whilst pregnant for indications such as pain or bipolar disorders (Vajda et al

Correspondence: Mervyn J Eadie
131 Wickham Tce, Brisbane,
QLD, Australia
Tel +61 7 3831 1704
Fax +61 7 3832 5608
Email m.eadie@mailbox.uq.edu.au

2003). Notification to the Registry may be initiated by the treating medical practitioner or by the patient herself. Further contact between the Registry and the patient is achieved by telephone conversation rather than by face-to-face interview because of the distances often involved between the patient's domicile and the Registry site. Registrants are interviewed by telephone on two occasions during pregnancy (at entry and at 7 months), within 1 or 2 months of giving birth, and also at one year after childbirth. Although the majority of patients have been enrolled before any investigation to exclude fetal abnormality was carried out, it has not always proved possible for patients to be notified to the Registry before this stage. Indeed, some women have not been notified to the Registry until after the outcome of the pregnancy is known. Such delayed notifications have been regarded as retrospective. The Registry data are stored in a secure database held at the Australian Centre for Clinical Neuropharmacology, Raoul Wallenberg Centre, The University of Melbourne at St Vincent's Hospital, Melbourne. The Ethics Committee of St Vincent's Hospital has approved the research and undertaken primary ethical responsibility for it. A small number of other local ethical committees have also been involved.

For the purposes of the present paper, all the data in the Registry relating to valproate use in pregnancy up to 31 December, 2003, have been analyzed, and some of the other data in the Registry have been employed for comparison purposes. Confidence interval (CI) analysis has been used throughout in assessing the statistical significance of results.

Results

At the time of the current analysis, the Registry database contained details of 560 completed pregnancies whose outcomes were known, including the birth of 10 sets of twins. In 520 of these pregnancies, AEDs had been taken, nearly always for the indication of epilepsy. There were also 40 pregnancies in epileptic women who were not receiving antiepileptic drug therapy who served as a control group. Of the 520 pregnancies treated with AEDs, 348 had received only AEDs other than valproate, and 172 had received valproate (always as the sodium salt) either as their sole antiepileptic agent (115 pregnancies) or in combination with other AEDs (57 pregnancies).

Spontaneous abortions had occurred in 3 of the 172 pregnancies that were exposed to valproate and in 13 of the 348 pregnancies exposed to AEDs other than valproate: a difference that was not statistically significant (1.74% vs 3.74%; odds ratio (OR) = 0.457: 95% CI = 0.129 – 1.63). Therapeutic induced abortions occurred in 6 of the 172 pregnancies exposed to valproate, but were significantly less frequent in the 348 pregnancies exposed to AEDs other than valproate, occurring in only one instance (3.49% vs 0.29%; OR = 12.5: 95% CI = 1.50 – 105). Four of the 6 induced abortions in the valproate-exposed women were for spina bifida detected prenatally. All of these induced abortions for known fetal abnormality have been included in the fetal malformation statistics to be discussed below. Stillbirths occurred in 3 of the valproate-exposed pregnancies, and in 4 of the 348 pregnancies exposed to epileptic drugs other than valproate (1.74% vs 1.15%; OR = 1.53: 95% CI = 0.338 – 6.90).

Fetal malformations that were detected in utero, recognized shortly after childbirth, or recognized at interview one year later, were present in a total of 26 of the 172 pregnancies in which valproate was taken, but in only 8 of the 348 pregnancies exposed to AEDs other than valproate (15.1% vs 2.30%; OR = 7.57: 95% CI = 3.35 – 17.1). Pregnancies resulting in fetal malformations were not statistically significantly more frequent amongst those associated with valproate intake than in the 40 pregnancies in the untreated epileptic women (15.1% vs 2.5%; OR = 6.95: 95% CI = 0.914 – 52.8). Pregnancies with fetal malformations occurred at very similar rates in women exposed only to AEDs other than valproate and in the untreated epileptic women (2.30% and 2.50%, respectively), though it should be noted that only small numbers of pregnancies not exposed to AEDs were available.

Five instances of spina bifida occurred in the valproate-exposed pregnancies (2.9%). Various other malformations involving different organ systems were encountered, whilst multiple separate malformations occurred in 7 of the 26 valproate-exposed pregnancies with malformations. More complete details are available elsewhere (Vajda et al 2004).

Pregnancies notified to the Registry after investigations had already been done to exclude intrauterine fetal abnormality, or notified only after the pregnancy was completed, might have produced relatively selected inclusion of pregnancies with abnormal fetal outcomes. Therefore, rates of pregnancies resulting in fetal malformations were also investigated in only the pregnancies that had been included in the Registry prospectively. There were 74 such valproate-exposed pregnancies and 148 pregnancies exposed to AEDs other than valproate. Fetal

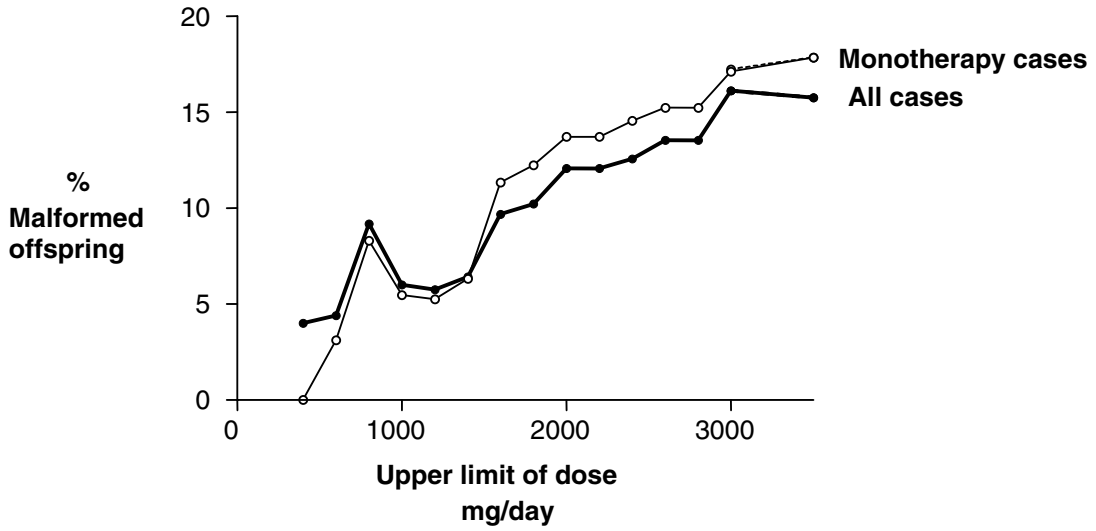

Figure 1 Cumulative rates of occurrence of pregnancies with malformations below various threshold daily valproate doses.

malformations occurred in 11 of the 74 prospectively notified valproate-exposed pregnancies, as compared with 1 of the 147 prospectively notified pregnancies exposed to AEDs apart from valproate. This was still a statistically significant difference in occurrence rates (15.1% vs 0.68%; OR = 25.5: 95% CI = 3.22 – 202). However, it was not a statistically significantly greater rate than the 1 in 40 rate in untreated epileptic pregnancies (15.1% vs 2.5%; OR = 6.81: 95% CI = 0.846 – 54.8).

Fetal malformations occurred in 20 of the 115 pregnancies exposed to valproate but to no other antiepileptic drug (ie, in valproate monotherapy), and in 6 of the 57 pregnancies exposed to valproate plus other AEDs (17.4% vs 10.5 %; OR = 1.79: 95% CI = 0.676 – 4.74). This difference in rates of pregnancies with fetal malformations was not statistically significant. Of the pregnancies exposed to valproate plus other antiepileptic drugs, lamotrigine was the other major drug involved. Fetal abnormalities were not more frequent with the valproate–lamotrigine combination (3 instances) than with valproate alone (9.1% vs 17.4%; OR 0.523: 95% CI = 0.146 – 1.87).

The effect of valproate dosage in the first trimester of pregnancy on the rates of occurrence of pregnancies with fetal malformations was examined by plotting the ratio of such pregnancies to the cumulative number of pregnancies exposed to valproate at or below a series of daily valproate doses of increasing magnitude (Figure 1). For pregnancies exposed to valproate alone and for all pregnancies exposed to valproate, the rates of those with fetal malformations remained about an average of 6%–7% until a threshold daily valproate dose of 1400 mg was reached. Above that dose, the rates of pregnancies with fetal malformations increased in an apparent dose-dependent manner. For all pregnancies exposed to valproate, the linear regression for malformation rate on doses at or below 1400 mg per day ($y = 4.294 + 0.00185$ dose; $r^2 = 0.1414$, $p = 0.463$) had a slope that was not statistically significantly different from zero; however, for doses above 1400 mg per day, the regression ($y = 8.234 + 0.00177$ dose; $r^2 = .0674$, $p = 0.007$) had a statistically significant upwards slope and an elevation that differed from that of the regression at lower doses ($p = 0.006$). At valproate doses below 1400 mg per day there were 7 pregnancies with fetal malformations in a total of 109 pregnancies (6.42%): at valproate doses above 1400 mg per day, 19 of 56 pregnancies resulted in fetal malformations (33.9%; OR = 0.134: 95% CI = 0.052 – 0.344). Figure 2 shows the rates of pregnancies with fetal malformations among pregnant women exposed to valproate at a series of dosage bands. This information is more relevant to the situation of the individual pregnancy in which the drug is taken. The fetal malformation risk after valproate exposure at doses of 1400 mg per day or less (6.42%) was compared with the risk in all pregnancies exposed to AEDs other than valproate (8 in 348, ie, 2.30%). The difference in rates (6.42% vs 2.30%) was just statistically significant (OR = 2.92: 95% CI = 1.03 – 8.24). However, the fetal malformed outcome risk (6.42%) at valproate doses of 1400 mg per day, or less, was not significantly different from the 2.5% risk in the 40 untreated epileptic pregnancies (OR = 2.68: 95% CI = 0.319 – 22.5). The point of particular

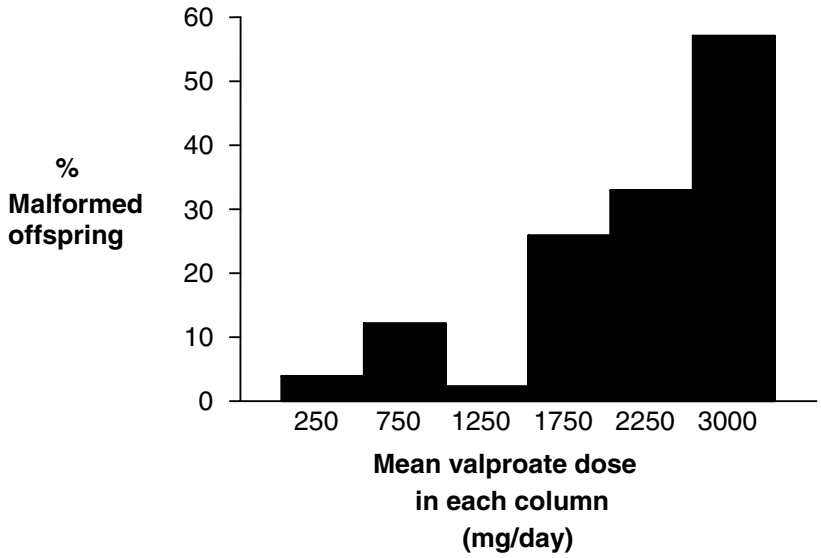

Figure 2 Rates of occurrence of pregnancies with malformations at various daily valproate doses.

clinical importance that emerged from this aspect of the study is that the relative risk of a malformed fetus in valproate-exposed pregnancies, as compared with pregnancies exposed to AEDs other than valproate, was statistically significantly increased relative to the risk for pregnancies exposed to AEDs other than valproate at all valproate doses, achieving an overall value of 7.02 (95% CI = 3.20 – 15.20) for all doses used. Further, the risk appeared to increase progressively once valproate doses exceeded 1400 mg per day.

The association between higher valproate doses and increasing rates of pregnancies with fetal malformation might have been due to higher drug doses being needed to treat more difficult-to-control epilepsy, with this epilepsy being responsible for the higher malformation rates. Therefore, rates of pregnancies with fetal malformation were compared in valproate-treated pregnancies in which bilateral convulsive seizures had occurred in early pregnancy (3 of 23 such pregnancies yielding fetal malformations) and in pregnancies free from convulsive seizures in their early months (22 of 146 such pregnancies yielding fetal malformations). The difference in rates (15.1% vs 13.0%; OR = 0.845: 95% CI = 0.231 – 3.09) was not statistically significant, suggesting that uncontrolled convulsive seizures were not likely to explain the malformation risk situation in valproate-exposed pregnancies.

The possibility of folic acid intake before or during pregnancy contributing to the risk of fetal malformations was assessed. No added folic acid had been taken in 10 of the 26 valproate-exposed pregnancies that resulted in fetal malformations, or in 47 of the 140 pregnancies exposed to AEDs other than valproate that did not result in malformations (38.5% vs 33.6 %; OR = 1.24: 95% CI = 0.521 – 2.94). This result suggested that folic acid intake probably did not protect against fetal malformations in pregnancies exposed to valproate.

Discussion

The present study has shown that valproate intake during pregnancy was associated with an apparently higher risk of fetal malformations than in epileptic pregnancies not exposed to AEDs; although, with small numbers being involved in the untreated pregnancy group, the difference was not statistically significant. Similar findings have emerged from previous studies (Kaneko et al 1992, 1999; Lindhout et al 1992; Kaneko and Kondo 1995; Samrén et al 1997, 1999; Morell 2003). However, the present study also demonstrated that exposure to valproate during pregnancy was associated with a significantly greater risk of fetal malformation than that associated with exposure to other AEDs in contemporary use. Earlier studies have sometimes contained data that point in this direction (Kaneko et al 1999; Samrén et al 1999), but this particular matter does not seem to have been subjected to statistical analysis previously. Although in the present study the fetal malformation risk in pregnancies exposed to AEDs apart from valproate appeared similar to that in untreated pregnancies in epileptic women, the latter conclusion was of necessity, based on a small dataset of untreated pregnancies and runs contrary to the general trend in the literature. It would seem unwise to rely on it unless it can be confirmed in a larger set of observations. Various malformations, including spina bifida, were found

to have occurred in the present valproate-exposed pregnancies, and folic acid intake did not seem to have conferred any definite protection against their occurrence.

The present study also suggested that the rate of pregnancies resulting in fetal malformation was relatively steady at sodium valproate doses up to about 1400 mg per day, but that there was a progressive and apparently dose-related increase in the rate once the daily drug dose exceeded this threshold. Such dose-dependence and an apparent cut-off between relatively safer and relatively hazardous doses of valproate have been noted by others (Samrén et al 1997, 1999; Kaneko et al 1999), who have set the cut-off at a dose of 1000 mg per day. However, it is not always clear whether this value referred to valproic acid, or to its sodium salt with its higher molecular weight. An earlier analysis of the portion of the present data that was then available found an apparent cut-off at a sodium valproate dose of 1100 mg per day (Vajda et al 2004). In the present study, there was a statistically significantly higher fetal malformation rate below the 1400 mg per day cut-off threshold for valproate dose as compared with the rate for AEDs other than valproate. However, there was no statistically significantly higher rate if the malformation rate in untreated epileptic pregnancies was used as the comparator. On the basis of the present study, it is difficult to know whether doses of valproate below 1000–1400 mg per day should be considered safe from the fetal point of view. At this stage in the accumulation of knowledge and until further collections of data are available and analyzed, perhaps with assessment of additional potential confounding factors, it may be prudent to regard any valproate dose in pregnancy as carrying more risk of fetal malformation than the risk of malformation that accompanies other commonly employed AEDs.

The existence of an apparent cut-off between a relatively steady malformed fetal risk at lower valproate doses and a progressively increasing risk at higher doses may seem surprising. However, the predominant pathway for valproate metabolism, at least in the non-pregnant state, tends to change from fatty acid β-oxidation to O-glucuronidation at about this same threshold dosage of valproate (Dickinson et al 1989). At such a dosage the body's β-oxidation capacity towards the drug appears to approach saturation. Therefore any additional valproate load may compete increasingly with endogenous fatty-acid derived substrates of β-oxidation, and accumulation of one or more of these substrates may harm the fetus.

In view of the substantial overall risks of malformed fetal outcomes associated with valproate exposure in pregnancy, the issue of the drug's use by pregnant women needs to be reappraised. It should be recognized that the following discussion is based on theoretical considerations arising from the above studies, and that there is, as yet, no evidence based on clinical experience that the courses of action suggested below will prove safer or otherwise more satisfactory for pregnant women or their offspring than current therapeutic practice.

If valproate at doses below 1400 mg per day, or perhaps 1000 mg per day, is considered safe in pregnancy, it appears reasonable to initiate therapy with the drug when it is indicated in women of childbearing potential so long as the dose can be kept below the increased malformation risk threshold value. Should such a dose prove clinically inadequate, another potentially suitable drug may be added to the valproate, particularly if the valproate dose can be reduced, or substituted. The data provided suggest that such AED combination therapy is unlikely to increase the fetal malformation risk. If ultimately there is no alternative but to use higher valproate doses, the patient must be made aware of the potential fetal hazards and the degree of risk, based on data such as that contained in Figure 2. If pregnancy is planned, and the valproate dose is below the threshold, no further action is needed. Doses above the threshold need to be reduced before pregnancy commences. If the dosage reduction results in loss of seizure control, suitable alternative AEDs may be added if they are available. If this proves unsatisfactory, the patient must be prepared to accept an increase in seizure frequency and perhaps severity whilst pregnant, or resume the higher valproate dose and either forego becoming pregnant, or accept the fetal malformation risks. Should the patient present already pregnant, the valproate dose should be reduced below what is believed to be the heightened malformation risk threshold and, if necessary, another drug added to control the patient's disorder. Prior to valproate dosage reduction, the patient should be made aware of the risks and the social implications of reduced seizure control. However, if the patient has presented after the first trimester of pregnancy, it would probably be too late for dosage reduction to benefit the fetus. The data of Figure 2 then provide a basis for advising the patient of the risk of malformation that exists and encourage patients to have an appropriate management plan in place for any subsequent pregnancy.

On the other hand, if valproate at any dose is regarded as unacceptably hazardous for the fetus, it can be argued

that the drug should not be prescribed for females of child-bearing potential until all suitable alternative agents have been tried. This would be the case even for juvenile myoclonic epilepsy or absence seizures, where valproate would otherwise be the drug of first choice. If valproate must be used its dose should be kept as low as possible. For women taking valproate and planning pregnancy, it would appear better to withdraw the drug and substitute an alternative. If a woman taking valproate presents in her first trimester of pregnancy, particularly if she presents early in the trimester, or if the valproate dose is high, it would appear preferable to cease intake of the drug quickly, though this exposes the mother to hazards even though another AED is substituted. Abrupt cessation of valproate intake should be carried out in hospital to reduce the dangers of withdrawal seizures and to permit more efficient treatment should they occur. If the initial presentation occurs after the first trimester of pregnancy, it would probably be too late for valproate withdrawal to be beneficial.

There are several well established alternative agents available with overall efficacies comparable to that of valproate in the case of partial (localization-related) epilepsy. In generalized epilepsies, where valproate is the most effective remedy, the alternative options are more limited. In disorders apart from epilepsy for which valproate might be used during pregnancy (eg, migraine prophylaxis, neuropathic pain, and bipolar disorder), principles similar to those discussed above would apply, though adapted to the different natural histories of the disorders being treated.

As further information accumulates, the considerations relating to the issues discussed above may alter, and decisions as to appropriate management may become easier and more soundly based on actual experience rather than on theoretical prediction. At the present time clinicians and their female patients face difficult judgments in balancing the advantages that valproate therapy may offer mothers or potential mothers, the disadvantages that its withdrawal may cause them, and the hazards its use may hold for their fetuses.

References

Anonymous. 1982. Valproate and malformations [editorial]. *Lancet*, ii:1313–14.

Dickinson RG, Hooper WD, Dunstan PR, et al. 1989. Urinary excretion of valproate and some metabolites in chronically treated patients. *Ther Drug Monit*, 11(Suppl 1):127–33.

Dravet C, Julian C, Legras C, et al. 1992. Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy: a French prospective cohort study. *Neurology*, 42(Suppl 5):75–82.

Hart YM. 2003. Should first-line treatment of epilepsy differ for males and females? *J R Coll Physicians Edinb*, 33(Suppl 11):11–21.

Janz D. 1975. The teratogenic risk of antiepileptic drugs. *Epilepsia*, 16: 159–69.

Kaneko S, Battino D, Andermann E, et al. 1999. Congenital malformations due to antiepileptic drugs. *Epilepsy Res*, 33:145–58.

Kaneko S, Kondo T. 1995. Antiepileptic agents and birth defects: incidence, mechanism and prevention. *CNS Drugs*, 3:41–55.

Kaneko S, Otani K, Kondo T, et al. 1992. Malformations in infants of mothers with epilepsy receiving antiepileptic drugs. *Neurology*, 42 (Suppl 5):68–74.

Lindhout D, Meinardi H, Meijer JWA, et al. 1992. Antiepileptic drugs and teratogenesis in two consecutive cohorts: changes in prescription policy paralleled by changes in pattern of malformations. *Neurology*, 42(Suppl 5):94–110.

Meadow SR. 1970. Congenital abnormalities and anticonvulsant drugs. *Proc R Soc Med*, 63:48–9.

Morrell MJ. 2003. Reproductive and metabolic disorders in women with epilepsy. *Epilepsia*, 48(Suppl 4):11–20.

Nau H, Hendrickx AG. 1987. Valproic acid teratogenesis. In: ISI atlas of science: pharmacology. p 52–6.

Omtzigt JGC, Los FJ, Grobbee DE, et al. 1992. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology*, 42(Suppl 5):119–25.

Samrén EB, van Duijn CM, Christiaens GC, et al. 1999. Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Ann Neurol*, 46:739–46.

Samrén EB, van Duijn CM, Koch S, et al. 1997. Maternal use of antieptileptic drugs and the risk of major congenital malformations: a joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia*, 38:981–90.

Vajda FJ, O'Brien TJ, Hitchcock A, et al. 2003. The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. *J Clin Neurosci*, 10:543–9.

Vajda FJ, O'Brien TJ, Hitchcock A, et al. 2004. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian Registry of anti-epileptic drugs in pregnancy. *J Clin Neurosci*. In press.