Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register

J I Morrow, S J Hunt, A J Russell, W H Smithson, L Parsons, I Robertson, R Waddell, B Irwin, P J Morrison and J J Craig

J. Neurol. Neurosurg. Psychiatry 2009;80;506-511; originally published online 31 Oct 2008;
doi:10.1136/jnnp.2008.156109

Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register

J I Morrow,[1] S J Hunt,[1] A J Russell,[2] W H Smithson,[3] L Parsons,[4] I Robertson,[5] R Waddell,[6] B Irwin,[6] P J Morrison,[7,8] J J Craig[1]

See Editorial Commentary, p 468

[1] Department of Neurology, Royal Group of Hospitals, Belfast, UK; [2] Department of Clinical Neurophysiology, Southern General Hospital, Glasgow, UK; [3] The Surgery, Escrick, York, UK; [4] Department of Neurology, St Albans City Hospital, St Albans, UK; [5] Obstetrics and Gynaecology Department, Lancashire Teaching Hospitals NHS Trust, Preston, UK; [6] Bostock House, Royal Group of Hospitals, Belfast, UK; [7] Department of Medical Genetics, Belfast City Hospital Trust, Belfast, UK; [8] School of Biological Sciences, University of Ulster, Coleraine, UK

Correspondence to:
Dr J I Morrow, Department of Neurology, Royal Group of Hospitals, Grosvenor Road, Belfast BT12 6BA, UK;
jim.morrow@belfasttrust.hscni.net

Received 18 June 2008
Revised 13 August 2008
Accepted 16 September 2008
Published Online First 31 October 2008

ABSTRACT

Objective: In the general population, folic acid supplementation during pregnancy has been demonstrated to reduce the frequency of neural tube defects (NTDs) and other major congenital malformations (MCMs). It is recommended that women with epilepsy contemplating pregnancy take supplemental folic acid because of the known antifolate effect of some antiepileptic drugs (AEDs). Here the aim was to determine the effectiveness of this practice.

Methods: This study is part of a prospective, observational, registration and follow-up study. Suitable cases are women with epilepsy who become pregnant and who are referred before outcome of the pregnancy is known. The main outcome measure is the MCM rate. Outcomes were analysed against folic acid exposure, malformation type and drug group for the most commonly used monotherapy AEDs.

Results: In 1935 cases reported to have received preconceptual folic acid, 76 MCMs (3.9%; 95% CI 3.1 to 4.9) and eight NTDs (0.4%; 95% CI 0.2 to 0.8) were identified. For 2375 women who were reported to have received folic acid but not until later in the pregnancy ($n = 1825$) or not at all ($n = 550$), there were 53 outcomes with an MCM (2.2%; 95% CI 1.7 to 2.9) and eight NTDs (0.34%; 95% CI 0.2 to 0.7).

Conclusions: The study supports the view that extrapolation from studies carried out in the general population to groups of women with epilepsy may be questionable. It may be that the increased risk of MCM recorded in this group occurs through mechanisms other than that of folic acid metabolism.

Preconceptual prescription of folic acid is recommended in women with epilepsy at a higher dose than is recommended to women without epilepsy contemplating pregnancy. Neural tube defects (NTDs) have been previously associated with exposure to antiepileptic drugs (AEDs) in utero.[1–3] In current clinical practice this abnormality is generally associated with exposure to sodium valproate or carbamazepine. The mechanism(s) by which exposure to these agents lead to NTDs are not known but may include an alteration in folate metabolism. Lamotrigine is a weak inhibitor of the enzyme dihydrofolate reductase; in human studies, exposure in non-pregnant subjects did not result in a significant change in red cell or serum folate levels.[4]

In the general population, folic acid supplementation has been shown to have a protective role in the primary prevention of neural tube and other congenital defects.[5–7] In a Medical Research Council (MRC) sponsored secondary prevention trial, women who had previously given birth to an infant with an NTD or who had a first degree relative with a child with an NTD, the prescription of a higher dose of folic acid (4 mg/day) preconceptually was associated with a 71% reduction in NTDs.[5]

Extrapolations have been made from these and other published studies to the epilepsy population. As the children born to women taking valproate and carbamazepine are considered to be at increased risk, current guidelines recommend that a daily dose of 5 mg of folic acid is prescribed preconceptually and continued at least until the end of the first trimester for all women taking AEDs. However, there have been very few studies specifically examining the effect of folic acid supplementation on the risk of NTDs and other congenital malformations in women taking AEDs. A published case study has demonstrated that even high dose folic acid (5 mg) taken preconceptually does not give absolute protection in this regard.[8]

Folate is a water soluble vitamin found in a variety of foodstuffs but there is no particularly good source except for liver. The paucity of folate rich foods eaten on a regular basis leads to a problem in achieving the higher folate status necessary to reduce the risk of development of NTDs in the fetus during pregnancy.[9] It has been estimated that the mean daily dietary intake of folate in the UK is 0.123 mg.[10]

Recent studies have demonstrated the presence of maternal antibodies that have the ability to bind to folic acid receptors and block the cellular uptake of folic acid. Such antibodies may therefore reduce the beneficial action of folic acid and hence produce a further rationale for preconceptual folic acid supplementation above low dietary intake.[11]

Daily dose supplementation of 5 mg of folic acid may well be more than is needed to achieve a maximum reduction of risk. The daily intake of approximately 0.4 mg/day is recommended for the general population. The larger dose however does not appear to cause any adverse effects unless the patient has pernicious anaemia (which should be considered prior to the prescription of folic acid).

Here we aim to determine the effectiveness of the practice of recommending supplemental preconceptual folic acid to women with epilepsy who are contemplating pregnancy.

Table 1 Details of offspring with a neural tube defect

Folic acid dose	PCFA	AED (total dose mg/day)	Major congenital malformation	Comments
5 mg	Yes	CBZ 150	Open myelomeningocele with associated intracranial changes of Arnold Chiari II with ventriculomegaly	Induced abortion
5 mg	Yes	CBZ 400	Sacral myelomeningocele	Induced abortion
5 mg	Yes	CBZ 600	Spina bifida	Induced abortion
5 mg	Yes	CBZ 1200	Spina bifida	Induced abortion
		LEV 3000		
400 μg	Unknown	CBZ 1200	Meningomyelocele and Arnold Chiari malformation	
		LTG 25		
		VPA1000		
Unknown	Unknown	CBZ 1200	Spina bifida	Induced abortion
		VPA 1000		
400 μg	Yes	LTG 550	Spina bifida	Induced abortion
5 mg	No	LTG 200	Spina bifida with patulous anus, lesion surgically closed	
		LEV 1000		
		VPA 1200		
		CLB 10		
Unknown	Unknown	LTG 300	Spina bifida, Arnold Chiari malformation upper spine	Induced abortion
		VPA 2000		
Unknown	Unknown	VPA dose U	Closed spina bifida and developmental delay	
5 mg	Yes	VPA 2000	Lumbosacral NTD, VSD, ASD, cleft palate	
5 mg	Yes	VPA dose U	Myelomeningocele	
400 μg	Yes	VPA 800	Spina bifida, hydrocephalus, dislocated hips, neurogenic bladder and bowel	
No	No	VPA 1500	Myelomeningocele L1–L2, hydrocephalus, bilateral talipies	
5 mg	No	VPA 1000	Ventriculomegaly, 3rd ventricle: 6 mm. 4th ventricle: 12 mm. Banana shaped cerebellum and obliterated cisterna magnum and sacral spina bifida. Arnold Chiari malformation. Thorax: pleural effusion	Induced abortion
400 μg	No	VPA 800	Spina bifida occulta	
5 mg	No	VPA 800	Large meningomyelocele was confirmed as was paralysis of lower limbs with fixed talipes	Induced abortion
5 mg	No	VPA 1500	Lumboscaral myelomeningocele with hydrocephalus	
5 mg	No	VPA 1200	Spina bifida and hydrocephalus	Induced abortion
5 mg	No	VPA 600	Lumbosacral myelomeningocele	
Unknown	Unknown	No AEDs	Myelomeningocele	Induced abortion

AED, antiepileptic drug; ASD, atrial septal defect; CBZ, carbamazepine; CLB, clobazam; LEV, levetiracetam; LTG, lamotrigine; MCM, major congenital malformation; NTD, neural tube defect; PCFA, preconceptual folic acid; VPA, sodium valproate; VSD, ventriculo-septal defect.

METHODS

This is a prospective, observational, registration and follow-up study which began in December 1996. Ethics approval was obtained from the North Thames multicentre research ethics committee and subsequently from all UK local research ethics committees. Written informed consent was obtained from all participants. Here we present our results analysed by folic acid use up until 31 January 2007.

Cases suitable for inclusion were defined as pregnant women with epilepsy, whether or not they were taking an AED, either in monotherapy or polytherapy, and who were referred to the register before the outcome of the pregnancy was known. Cases where any prenatal test (fetal ultrasound, blood test) had shown an abnormality, and cases resulting in a pregnancy loss in which an abnormality had been identified before referral to the register had been made, were excluded. Cases that were on no AEDs during the first trimester but then had second or third trimester exposure to an AED were also excluded. Cases with exposure to more than one AED during the first trimester, or who had additional AEDs starting in the second or third trimesters, were counted as polytherapy exposures. Folic acid supplementation (dose and timing of use) were recorded at registration.

Cases were referred to the register by neurologists, epilepsy nurse specialists, obstetricians and midwives, general practitioners and other health care professionals caring for women with epilepsy, and from women with epilepsy themselves through our freephone (0800 3891248) or by downloading registration forms from our website (www.epilepsyandpregnancy.co.uk).

Information was collected at registration from the referring source and as required from any other relevant health care professionals. Details collected included general demographic information, epilepsy details, including the cause of the epilepsy if known, seizure types and frequency, AED exposure details up to 3 months before conception and during the pregnancy up to the date of referral, with any changes made, and other drug exposure details, including folic acid prescription with details of dose and whether started preconceptually. Outcome data were collected at 3 months after the expected date of delivery by sending the patient's general practitioner a standardised questionnaire for completion. Information collected at this time included changes to AEDs during pregnancy, previous pregnancy details, relevant family history, current pregnancy details, including the results of prenatal testing, and details on

current pregnancy outcome. At this time any others (eg, clinical geneticist, paediatrician) who had been identified either during the pregnancy or at follow-up were also contacted for further information.

Outcomes were classified by one of the authors (PJM) into those without birth defects, those with major congenital malformations (MCMs) and those with other defects (minor defects, chromosomal disorders and single gene defects). For each of these categories, outcomes were further subdivided into live births and pregnancy losses (spontaneous pregnancy losses or induced abortions).

MCM was defined as an abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered during the first 6 weeks of life. Significant treatment was deemed to include surgical intervention for a defect in a major organ or system requiring repair or substantive medical treatment to avoid repair. Disorders not conforming to this definition were assigned as minor malformations based on the definitions and lists of disorders in the EUROCAT registry.[12]

The MCM rate was calculated as (total number of live births with an MCM) + (total number of pregnancy losses with an MCM) ÷ (total number of live births) + (total number of pregnancy losses with an MCM). Spontaneous pregnancy losses and induced abortions where no abnormalities were reported were not included for analysis as we do not know if they were examined in detail and therefore cannot know the outcome. The total numbers presented for each group are therefore either the total number of outcomes or the total number of informative outcomes—that is, excluding pregnancy losses with no abnormalities reported.

For each MCM rate, 95% confidence intervals (CI) were calculated, based on Wilson, using confidence interval analysis for Windows.[13] Probability (p) values of <0.05 were considered significant. Calculations were done using SPSS, V.16. Full details on study methodology have been reported previously.[14]

RESULTS

Folic acid prescription

Of the total 4680 pregnancies in the study, it was reported that in 4130 cases (88.3%) folic acid had been prescribed by the time of registration. In 1935 cases (41.3%) it was reported that folic acid had been commenced preconceptually. In 1825 cases (39.0%), folic acid had not been prescribed until later in the pregnancy and 550 (11.8%) had not received any folic acid by the time of registration. In 370 cases (7.9%) the timing of the initiation of the prescription of folic acid was uncertain.

Of 4130 women who received folic acid at any time prior to or during the pregnancy, 2927 (70.9%) received the recommended higher dose (5 mg) and 881 (21.3%) received the lower dose (400 μg). In 322 cases (7.8%) the dose taken was not recorded.

Table 2 Major congenital malformations in the entire evaluable cohort.

MCM group	MCMs in PCFA group (n = 1935) (n (%) (95% CI))	MCMs in no PCFA group (n = 2375) (n (%) (95% CI))
All	76 (3.9) (3.1–4.9)	53 (2.2) (1.0–3.3)
NTD	8 (0.4) (0.2–0.8)	8 (0.3) (0.2–0.7)
Oral clefts	8 (0.4) (0.2–0.8)	11 (0.5) (0.3–0.8)
Hypospadias	11 (0.6) (0.3–1.0)	6 (0.3) (0.1–0.6)
Cardiac	19 (1.0) (0.6–1.5)	11 (0.5) (0.3–0.8)

MCM, major congenital malformation; NTD, neural tube defect; PCFA, preconceptual folic acid.

Of those 1935 who did receive preconceptual folic acid, 1518 (78.4%) received the recommended higher dose (5 mg), 353 (18.2%) received the lower dose (400 μg) and in 64 cases (3.3%) the dose taken was not recorded.

In the UK, current guidelines recommend preconceptual prescription of 5 mg of folic acid daily. Of the 4680 registrations, 1518 (32.4%) had received this recommended higher dose (5 mg) of folic acid preconceptually.

A total of 3391 (72.5%) registrations were exposed to monotherapy, with 963 (20.6%) exposed to polytherapy: 326 (7.0%) were not exposed to AEDs. The major congenital malformation rate was higher for polytherapy exposed pregnancies (6.0%) than to monotherapy exposed pregnancies (3.6%). We found that 51.4% of patients on monotherapy received folic acid (at any dose) preconceptually compared with only 15.0% of polytherapy exposures.

Major congenital malformations

For the 4680 registrations, a total of 161 MCMs were identified (3.4%; 95% CI 3.0 to 4.0). In 370 cases (7.9%), who were receiving folic acid at registration, there was uncertainty regarding the timing of the original prescription of folic acid and this group was excluded from comparison of the results.

In the remaining 4310 cases, 1935 (44.9%) women were reported to have received preconceptual folic acid (either 5 mg or 400 μg). In 2375 (55.1%) cases, folic acid had not been taken preconceptually. In 1825 of these women, folic acid (5 mg or 400 μg) had been prescribed but commenced after conception in whom 43 MCMs were reported (2.4%; 95% CI 1.8 to 3.4). In 550 cases folic acid had not been taken by the time of registration in whom 10 MCMs were reported (1.8%; 95% CI 1.0 to 3.3).

For those women who took preconceptual folic acid, the odds ratio for having a baby with an MCM was 1.76 (95% CI 1.25 to 2.56) ($p = 0.001$).

Neural tube defects

For the entire cohort ($n = 4680$), 21 NTDs were identified among the abnormal outcomes (0.45%; 95% CI 0.3 to 0.7). Table 1 details those cases with NTDs against drug exposure and folate prescription.

Within the group of 1935 women who had received preconceptual folic acid, eight NTDs were reported. Six of these eight women had received the 5 mg dose (0.4%; 95% CI 0.18 to 0.86) and two the 400 μg dose preconceptually (0.57%; 95% CI 0.16 to 2.04).

Of 2375 women who did not receive preconceptual folic acid there were also eight cases of NTDs in offspring. Only in one case was it reported that no folic acid had been prescribed or taken (0.18%; 95% CI 0.0 to 1.0).

Oral clefts

For the entire cohort ($n = 4680$), 26 oral clefts were identified among the abnormal outcomes (0.56%; 95% CI 0.4 to 0.8).

Within the group of 1935 women who had received preconceptual folic acid, eight oral clefts were reported. Five offspring had been exposed to AED use as monotherapy with the remainder exposed to polytherapy.

Of 2375 women who had not received preconceptual folic acid there were 11 cases of oral clefts in offspring. Ten of these offspring had been exposed to monotherapy and one to polytherapy. In only one case was it reported that no folic acid had been prescribed or taken (0.18%; 95% CI 0.0 to 1.0)

Table 3 Cases of neural tube defects by monotherapy drug group

Drug	NTDs in PCFA group (n (%) (95% CI))	NTDs in no PCFA group (n (%) (95% CI))
CBZ	3 (0.5) (0.0–1.5)	0 (0.0) (0.0–0.8)
LTG	1 (0.2) (0.0–0.9)	0 (0.0) (0.0–1.1)
VPA	3 (0.8) (0.3–2.2)	7 (1.7) (0.7–3.4)

CBZ, carbamazepine; LTG, lamotrigine; NTD, neural tube defect; PCFA, preconceptual folic acid; VPA, sodium valproate.

Table 4 Cases of major congenital malformations by monotherapy drug group

Drug	MCMs in PCFA group (n (%) (95% CI))	MCMs in no PCFA group (n (%) (95% CI))
CBZ	14 (2.4) (1.4–4.0)	11 (2.3) (1.3–4.0)
LTG	16 (2.5) (1.5–4.0)	7 (1.9) (0.9–3.9)
VPA	21 (5.3) (3.5–8.0)	18 (4.3) (2.8–6.8)

CBZ, carbamazepine; LTG, lamotrigine; MCM, major congenital malformation; PCFA, preconceptual folic acid; VPA, sodium valproate.

Hypospadias

Within the total (n = 4,680) pregnancy outcomes, 19 cases of hypospadias were identified (0.40%; 95% CI 0.3 to 0.6). Within the group of 1935 women who were reported to have received preconceptual folic acid, there were 11 reported cases. Within the other group of 2375 women who were not reported to have received preconceptual folic acid, there were six reported cases of hypospadias.

Cardiac abnormalities

Thirty five cardiac MCMs were reported from the total outcome group (0.74%; 95% CI 0.5 to 1.0). Nineteen of these abnormalities occurred in women who had been reported to have received folic acid preconceptually. Eleven cases occurred in women who had been reported not to have received preconceptual folic acid. Table 2 depicts these results.

Folic acid prescription by individual AED

In all, 3391 cases (72.4%) had been exposed to a single AED in pregnancy, 963 (20.6%) to more than one AED and 326 (7.0%) were reported to have epilepsy but were not exposed to any AEDs during their pregnancy. The three most frequently reported monotherapy exposures were to carbamazepine (n = 1176, (34.7%)), lamotrigine (n = 1078, (31.8%)) and sodium valproate (n = 894, (26.4%)).

In the carbamazepine monotherapy group, 584 patients were recorded as receiving preconceptual folic acid (either 5 mg or 400 μg), 485 patients were reported not to have received folic acid until later in the pregnancy or at all and in 107 there was uncertainty regarding its prescription.

In the sodium valproate monotherapy group, 395 patients were recorded as receiving preconceptual folic acid (either 5 mg or 400 μg), 415 patients did not receive folic acid until later in the pregnancy or at all and in 84 cases there was uncertainty regarding its prescription.

In those that did receive preconceptual folic acid, there were three recorded NTDs against seven in the group that did not receive preconceptual folic acid (in only one of these cases was it reported that no folic acid had been prescribed by the time of registration).

For NTDs in this subgroup, the relative risk in those that did receive folic acid (at any dose) preconceptually was 0.45 (95% CI 0.12 to 1.73) compared with those who did not receive preconceptual prescription. The number of cases needed to treat to benefit one case was 108 (95% CI 36.4 to 131.3).

In the lamotrigine monotherapy group, 638 patients were recorded as receiving preconceptual folic acid (either 5 mg or 400 μg), 362 patients did not receive folic acid until later in the pregnancy or at all and in 78 cases there was uncertainty regarding its prescription.

These results are shown in tables 3 and 4.

DISCUSSION

Folic acid is important for the biosynthesis of many compounds, including amino acids.[15] The possibility that maternal folate status might be implicated in NTD was raised in 1965 when Hibbard and Smithells showed that a test indicating lack of folate or disturbed folate metabolism (the FIGLU test) was more often positive in women carrying a fetus with an NTD than in controls.[16] This finding stimulated a number of studies investigating the role of folic acid in relation to NTDs.

Randomised controlled trials, controlled trials and non-controlled intervention studies in high and low risk patients have reported that folic acid supplementation taken before or early in pregnancy reduced the incidence of primary and recurrent NTDs and other congenital abnormalities.[5 6 17] The MRC vitamin study, in particular, demonstrated a substantial reduction in the incidence of NTD with periconceptual folic acid supplementation (4 mg).[5] The recurrence rate in the folic acid groups was 1.0% and in the non-folic acid groups it was 3.5% (odds ratio 0.29; 95% CI 0.12 to 0.71).

There has also been evidence in the general population to suggest that folic acid may protect against other congenital anomalies such as oral clefts, cardiac abnormalities and urinary tract defects.[7 18–22] In contrast, one study has questioned the beneficial effect of folic acid in preventing congenital abnormalities of the non-neural tube type.[23]

The biological mechanism underlining the association of the AEDs in congenital abnormalities, however, is essentially unknown. Certain AEDs, including carbamazepine, phenobarbitone, phenytoin and primidone, influence folic acid absorption.[24] Carbamazepine and phenytoin may also induce the formation of toxic intermediates which may interfere with DNA synthesis and organogenesis.[25] However, whether this is affected by folic acid supplementation remains essentially unknown.

The rationale for the recommendation of folic acid supplementation in women with epilepsy taking AEDs is simply from the recognition that these women are at higher risk of MCMs in general and NTDs in particular. However, it is being increasingly recognised that the NTDs seen in the epilepsy population may differ significantly from those of the general population.[26]

The recommended dose of folic acid for women with epilepsy is also under debate. In the randomised and non-randomised trials published in the 1990s, 4 mg/day, 800 μg/day or 400 μg/day were prescribed. Women with epilepsy in the UK are commonly advised through published guidelines to take 5 mg of folic acid per day, simply because they are considered a high risk group and the only available formulations are a 400 μg and a 5 mg tablet.

Women with epilepsy are recognised as a high risk group, with regard to MCM, and national guidelines consistently recommend preconceptual prescription of high dose (5 mg) folic acid.[27–29] The rates of folic acid prescription in this current study may be taken to reflect the availability or effectiveness of preconceptual counselling in the UK. It has been estimated that 60% of pregnancies (in the general population) in the UK are

planned but a background rate of only 30% preconceptual folic acid prescription has been reported.[10] In this current study of women with epilepsy, 41.3% of women received folic acid preconceptually (but only 32% received the higher (5 mg) recommended dose). It may, therefore, be argued that these figures suggest that we are not as yet achieving the levels of awareness of the importance of preconceptual counselling and of pregnancy planning that this high risk group deserves.

The fact that significant numbers of women did not receive preconceptual folic acid has allowed for a comparison of outcomes between groups to be made. The pregnancy outcomes of those patients that were reported to have received preconceptual folic acid (at any dose) were compared with those that did not receive it at all or received it only after pregnancy was confirmed.

Given the very low incidence of specific malformations, the overall numbers of outcomes (n = 4680), although the largest in the area, may still be considered small. The study does appear to confirm the increased risk, above that of the general population, for the offspring of women with epilepsy of MCMs in general and some specific abnormalities in particular. The results from this study, however, do not appear to support the view that folic acid has a significant protective effect in this patient group. In fact, paradoxically, those patients that did receive preconceptual folic acid in this cohort appeared more likely to have a child with an MCM than those that did not receive folic acid until later in the pregnancy or at all (3.9% vs 2.2%) (odds ratio 1.8; 95% CI 1.2 to 2.5). Even if one makes the assumption that in those 370 patients in whom there was uncertainty regarding the timing of the initiation of the folic acid prescription, did not in fact receive it preconceptually, then the MCM rate in the non preconceptual group rises to 3.1% (95% CI 2.6 to 3.5) and any statistical difference between the two groups is lost.

Registrations that were exposed to monotherapy were much more likely to have received preconceptual folic acid than polytherapy exposures. Given that the major malformation rate for polytherapy exposures was higher than for monotherapy exposure, this does not explain the paradoxical findings, as had the difference between monotherapy and polytherapy folic acid prescription been important then this would have been expected to have biased the results towards a positive result in favour of the protective effect of folic acid.

For individual malformations, including NTDs, the difference in rates between those that did and those that did not receive preconceptual folic acid were small, not statistically significant and certainly not of the order seen in studies of the general population.

With regard to the individual commonly used AED therapies, the overall numbers of cases of NTDs were small and only in the sodium valproate group (the group usually considered at highest risk) did there appear to be any trend towards a reduction in relative risk (0.45 (0.12 to 1.73) for NTDs but not for MCMs in general) associated with the preconceptual prescription of folic acid.

Few other studies have assessed the effect of folic acid supplementation among women treated with AEDs. In previous studies, exposure to folic acid antagonists was associated with an increased risk of NTDs, cardiovascular defects, oral clefts and urinary tract abnormalities. Folic acid supplementation did not appear to modify the effect of exposure to AEDs and these congenital anomalies.[24 30]

Others have investigated the association between folic acid antagonist exposure in the first 10 weeks of pregnancy and the prevalence of congenital abnormalities. No increased prevalence of congenital abnormalities were found with folic acid antagonists in general, but exposure to AEDs (carbamazepine, phenobarbitone, phenytoin, primidone, valproate and lamotrigine) increased the prevalence of the specific abnormalities, especially heart anomalies, NTDs and limb defects. Once again, folic acid supplementation was not shown to modify the association between the AEDs and these congenital abnormalities.

In summary, therefore, given the current guidelines, preconceptual folic acid prescription may be regarded as a measure of the availability and/or effectiveness of preconceptual planning in women with epilepsy. If that premise is accepted, then this study suggests that despite the known or perceived risks of epilepsy, AEDs and pregnancy, the majority of women with epilepsy in the UK may not be receiving and/or recalling preconceptual advice.

The study also brings into question the perceived protective effects of preconceptual folic acid supplementation in this patient group. The study supports the view that direct extrapolation from studies carried out in the general population to groups of women with epilepsy, treated with AEDs, may be questionable. It may be that the increased risk of major congenital malformations in general and NTDs in particular recorded in this group may occur through mechanisms other than that of folic acid metabolism. Larger studies in this field will be required to clarify these issues.

Acknowledgements: We thank all the doctors, midwives and epilepsy specialist nurses who recruited patients and the women with epilepsy who gave their consent to take part in the study and provided outcome data.

Funding: We are grateful to the Epilepsy Research Foundation and Epilepsy Action for their support of this project. The study was made possible by a research grant from the Epilepsy Research Foundation and a number of educational grants from pharmaceutical companies (Eisai, Glaxo-Smith-Kline, Janssen-Cilag, Pfizer, Sanofi-Aventis and UCB-Pharma). An internet based website detailing the aims of the UK Epilepsy and Pregnancy Register was made possible by a grant from Glaxo-Smith-Kline and UCB-Pharma.

Competing interests: JIM, SJH, AJR, WHS, LP, PJM, RW, BI and JJC have attended meetings with the support of various pharmaceutical companies, including Eisai, Glaxo-Smith-Kline, Janssen-Cilag, Pfizer, Sanofi-Aventis and UCB-Pharma. JJC, LP, PJM and JIM have given lectures at the bequest of pharmaceutical companies for which they have received honoraria. IR reports no conflicts of interest.

Ethics approval: Ethics approval was obtained from the North Thames multicentre research ethics committee and subsequently from all UK local research ethics committees.

REFERENCES

1. **Rosa FW.** Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991;**324**:674–7.
2. **Omtzigt JG,** Los FJ, Grobbee DE, *et al*. The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. *Neurology* 1992;**4**:119–25.
3. **Samrén EB,** van Duijn CM, Koch S, *et al*. 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.
4. **Sander JW,** Patsalos PN. An assessment of serum and red blood cell folate concentrations in patients with epilepsy on lamotrigine therapy. *Epilepsy Res* 1992;**13**:89–90.
5. **MRC Vitamin Study Research Group**. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;**338**:131–7.
6. **Czeizel A,** Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;**327**:1832–5.
7. **Czeizel AE,** Tímár L, Sárközi A. Dose-dependent effect of folic acid on the prevention of orofacial clefts. *Pediatrics* 1999;**104**:66.
8. **Craig J,** Morrison P, Morrow J, *et al*. Failure of periconceptual folic acid to prevent a neural tube defect in the offspring of a mother taking sodium valproate. *Seizure* 1999;**8**:153–4.
9. **Cuskelly GJ,** McNulty H, Scott JM. Effect of increasing dietary folate on red cell folate: implications for prevention of neural tube defects. *Lancet* 1999;**347**:657–9.
10. **EUROCAT**. *Prevention of neural tube defects by periconceptual folic acid supplementation in Europe*. Special report. Brussels: European Union, 2003.
11. **Rothenberg SP,** da Costa MP, Sequeira JM, *et al*. Autoantibodies against folate receptors in women with pregnancy complicate by a neural-tube defect. *N Engl J Med* 2004;**350**:134–42.

12. **de Wals P,** Mastroiacovo P, Weatherall JAC. *et al*. *EUROCAT guide for the registration of congenital anomalies*. Brussels: European Union, 1984.
13. **Wilson EB.** Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc* 1927;**22**:209–12.
14. **Morrow J,** Russell A, Guthrie, *et al*. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;**77**:193–8.
15. **Hillman R.** Hematopoietic agents. In: Hardman J, Limbird L, Gilman A, eds. *Goodman and Gilman's. The pharmacological basis of therapeutics*. New York: McGraw-Hill, 2001:1503–13.
16. **Hibbard E,** Smithells R. Folic acid metabolism and human embryopathy. *Lancet* 1965;**i**:1254.
17. **Berry RJ,** Li Z, Erickson JD, *et al*. Prevention of neural-tube defects with folic acid in China. China–US Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med* 1999;**341**:1485–90.
18. **Shaw GM,** O'Malley CD, Wasserman CR, *et al*. Maternal peri-conceptual use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. *Am J Genetics* 1995;**59**:536–45.
19. **Tolarova M,** Harris J. Reduced recurrence of orofacial clefts after periconceptual supplementation with high dose folic acid and multivitamins. *Teratology* 1995;**51**:71–8.
20. **Werler M,** Hayes C, Louik C, *et al*. Multivitamin supplementation and risk of birth defects. *Am J Epidemiol* 1999;**150**:675–82.
21. **Botto LD,** Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. *Am J Epidemiol* 2000;**151**:862–77.
22. **Li D,** Daling J, Mueller B, *et al*. Periconceptual multivitamin use in relation to risk of congenital urinary tract anomalies. *Epidemiology* 1995;**6**:212–18.
23. **Kallen B,** Olausson P. Use of folic acid and delivery outcome: a prospective registry study. *Reprod Toxicol* 2002;**16**:327–32.
24. **Hernandez-Diaz S,** Werler M, Walker A, *et al*. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med* 2000;**343**:1608–14.
25. **Lewis D,** Van Dyke D, Stumbo P, *et al*. Drug and environmental factors associated with adverse pregnancy outcomes. Part 1: Antiepileptic drugs, contraceptives, smoking and folate. *Ann Pharmacother* 1998;**32**:802–17.
26. **Morrow J,** Craig J. Anti-epileptic drugs in pregnancy: current safety and other issues. *Expert Opin Pharmacother* 2003;**4**:445–56.
27. **Crawford P,** Lee P. Gender difference in management of epilepsy: What women are hearing. *Seizure* 1999;**8**:135–9.
28. **Scottish Intercollegiate Guidelines Network (SIGN)**. *Diagnosis and management of epilepsy in adults: A National clinical guideline*. Edinburgh: Scottish Intercollegiate Guidelines Network, 2003.
29. **National Institute for Clinical Excellence (NICE)**. *The diagnosis and management of the epilepsies in adults and children in primary and secondary care*. London: NICE, 2004.
30. **Hernandez-Diaz S,** Werler M, Walker A, *et al*. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol* 2001;**153**:961–8.