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Antiepileptic drugs and foetal malformation: analysis of 20 years of data in a pregnancy register

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ABSTRACT

Purpose: This paper reports additional data supplementing earlier publications based on Australian Pregnancy Register (APR) data.

Method: Over 20 years, the APR has collected Information on pregnancies in Australian women with epilepsy (WWE), untreated WWE and those taking AEDs for other indications. Contact is by telephone, at set intervals. Treatment is not interfered with. Data are analysed using conventional statistical techniques, confidence interval methods, and logistic regression.

Results: By 2018, the APR contained details of 2148 pregnancies. AEDs were taken throughout 1972 of the pregnancies (91.8%). The remaining 176 (8.2%) did not receive AEDs, at least early in pregnancy.

There were (i) dose-related increased incidences of pregnancies carrying foetal malformations associated with maternal intake of valproate and topiramate when topiramate was a component of AED polytherapy ($P < .05$), (ii) a similar dose-related trend in relation to carbamazepine intake, (iii) no evidence that levetiracetam and lamotrigine were unsafe from the foetal standpoint, (iv) insufficient data to permit conclusions regarding teratogenicity in relation to other AEDs, and (v) no evidence that pre-conception folate supplementation reduced the hazard of AED-associated foetal malformation. AED polytherapy did not increase foetal hazard unless valproate or topiramate was involved in the AED combination. Genetic factors probably contributed to the malformation hazard. Seizures occurring in earlier pregnancy probably did not contribute to the malformation hazard.

Conclusions: If it were not for the importance of maintaining seizure control, the above findings suggest that it would be better to avoid using certain AEDs, particularly valproate and topiramate, during pregnancy.

1. Introduction

For almost 20 years ago the Australian Register of Antiepileptic Drugs in Pregnancy (APR) has collected data concerning intrauterine exposure to such drugs and foetal malformations. Over this time, certain aspects of the data, especially material relating to foetal malformations, have been examined at regular intervals, to permit timely publication of findings of potential clinical importance, but no report concerning the whole data collection has been published. Subsequently additional data relevant to some of the earlier publications have been accumulated. It now seems worth reanalysing all the data currently held in the APR to update and, where necessary, modify the earlier findings and interpretations.

2. Materials and methods

2.1. Recruitment policiess

The APR has recorded information on the courses and outcomes of pregnancy in Australian women taking AEDs for any indication, though nearly always for epilepsy, and in Australian women with epilepsy not treated with AEDs in at least the first half of pregnancy.

The APR's aims and activities have been made known to such women, to those concerned with their medical management, and to various relevant institutions and societies, employing various means including word-of-mouth transmission, literature publications, and formal public advertising mechanisms when feasible financially. Pregnant women who are interested in enrolling are invited to contact the APR by telephone. If their interest continues, all further contact is

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by telephone, at the initial contact, at seven months of pregnancy, within the first month after childbirth, and a year later. Relevant details are stored in two Microsoft Access databases which can be linked. One contains women's names and contact details only, the other clinical details concerning the current and any previous pregnancies and maternal health. APR personnel neither offer treatment advice nor attempt to otherwise influence treating medical personnel, but confirm with the latter and through hospital records, the correctness of information supplied by the enrolled women.

2.2. APR housing and ethics oversight

During its existence the APR has been housed in various institutions in Melbourne (St. Vincent's Hospital, Monash University, the Royal Melbourne Hospital), depending on the institutional affiliations of those involved in its operation. The research ethics committees of these institutions have undertaken ethics oversight of the APR, depending on where it was housed.

2.3. Support / funding

Over the years the APR has received financial support from various pharmaceutical companies (see Acknowledgements section) and, in recent years, from the Epilepsy Society of Australia and Epilepsy Action.

2.4. Data handling/analysis

Data from the APR database have been transferred to Microsoft Excel spreadsheets and analysed using conventional simple statistical techniques, mainly confidence interval methods, and logistic regression.

3. Results

3.1. The pregnancies studied

By the beginning of 2018, the APR contained details of 2148 pregnancies, 43 involving twins that had occurred in 1671 women. Contact with the woman concerned was lost during 23 pregnancies, so that data for 2125 pregnancies with known outcomes were analysed. By the end of the first year after pregnancy, the women involved in 1882 pregnancies were contactable. The women in the 96 pregnancies that did not result in live births were not contacted, 28 had not reached the one-year post-partum stage and the remainder had either rejected further participation, or were uncontactable. Except where indicated, the analyses that follow are based on numbers of pregnancies with known outcomes at the end of pregnancy, and not on numbers of foetuses or live births, or numbers contacted at the end of the post-partum year.

The time-course of the accumulation of pregnancies in the APR is shown in Fig. 1.

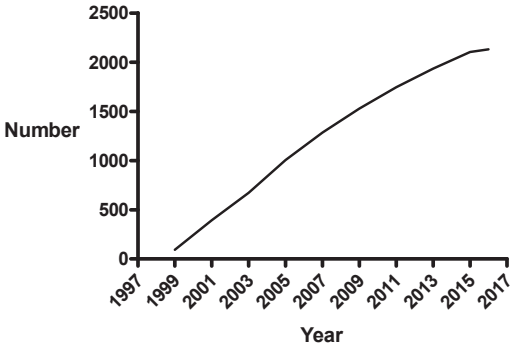

Fig. 1. Time course of accumulation of pregnancies in the APR.

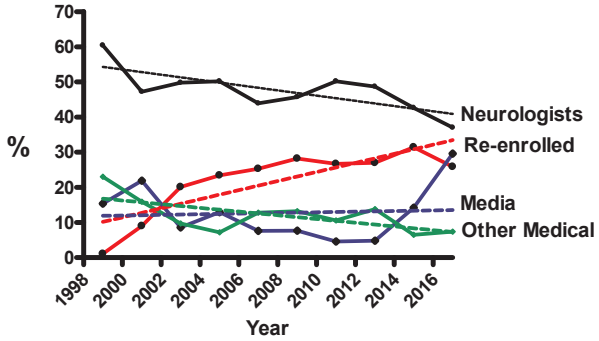

Fig. 2. Changes with time on the proportions of pregnancies referred to the APR by neurologists, by other medical sources, because of information available in the media and by women re-enrolling.

Throughout, Australian neurologists were the major source of referral to the APR, but with a progressively increasing contribution from women referring themselves back to the APR in subsequent pregnancies (Fig. 2). Assuming similar fertility rates to other Australian women, only 8–9% the expected pregnancies of women with epilepsy in the country probably were captured by the APR [1].

Pregnancies were enrolled at various stages of intrauterine foetal development. As recorded, the dates of the last menstrual period were sometimes physiologically improbable, acceptable data being available for only 1872 pregnancies. In the first 90 days of pregnancy, 19.7% of the pregnancies were enrolled, with another 50.3% added in the second 90 days.

3.2. The AEDS involved

AEDs were taken throughout 1972 of the 2148 pregnancies (91.8%), while the remaining 176 (8.2%) were not exposed to AEDs in at least the first half of pregnancy. Women with epilepsy accounted for 98.3% of both the 1972 AED-exposed pregnancies and the 176 AED-unexposed ones. AEDs were prescribed for miscellaneous indications in the remainder. AED intake had ended shortly before pregnancy, apparently in preparation for it, in 68 of the 176 AED-unexposed pregnancies. There had already been long periods without AED intake before pregnancy in the remaining 108, some 38% of the former sub-group and 34% of the latter, resumed AED intake by the seven-month stage of pregnancy.

The AED-exposed pregnancies did not differ statistically significantly from the AED-unexposed ones in relation to: maternal age at enrolment (31.02 ± s.d. 4.85 *versus* 30.96 ± s.d. 4.65 years; difference = 0.06 years, 95% C.I. -0.69, +0.81 years); duration of epilepsy (16.75 ± s.d. 8.38 *versus* 17.95 ± s.d. 9.46 years; difference = -1.20 years, 95% C.I. -2.57, +0.17 years); time seizure free before pregnancy 2.53 ± s.d. 3.67 *versus* 3.48 ± s.d. 6.37 years; difference -0.95 years, 95% C.I. + 1.59, -0.31 years); proportions of first pregnancies (40.6% *versus* 44.3% ; O.R. = 0.86, 95% C.I. 0.63, 1.17); previous pregnancies associated with foetal malformations (4.9% *versus* 2.0% ; O.R. = 2.46, 95% C.I. 0.59, 10.22).

Multiple AEDs (polytherapy) were taken in at least the earlier months of pregnancy in 555 of the AED-exposed pregnancies (28.1%), AED monotherapy in the remainder. The individual drugs taken in monotherapy, and in all AED-exposed pregnancies, are listed in Table 1. There were too many individual drug combinations in the polytherapy group, many of them containing too few pregnancies, for worthwhile further analysis. However, valproate participated in 211 of the combinations (38.0%) and topiramate in 99 (16.2%), both drugs being present in 24 of the combinations. AED combinations involved two drugs in 82.0%, three in 14.1%, four in 2.2% and five 0.9% in the remainder

The proportions of all pregnancies managed by AED treatment, and by treatment in monotherapy, did not change statistically significantly over the 20 years surveyed (Fig. 3). Over this time the use of valproate

Table 1
Pregnancy numbers associated with each AED used in monotherapy and as monotherapy plus polytherapy, rates of occurrence of pregnancy involving malformed foetuses associated with individual AEDs used in monotherapy in at least the first half of pregnancy, and the risk of AED-exposed pregnancies bearing malformed foetuses relative to that in AED-unexposed pregnancies (no AEDs).

AED	Monotherapy					All pregnancies
	N =	Malfs	Malf %	R.R.	95% C.I.	N =
No AEDs	176	5	2.8			
Valproate	290	43	14.8	5.22	2.11, 12.95	501
Carbamazepine	409	24	5.9	2.07	0.80, 5.33	603
Lamotrigine	406	20	4.9	1.75	0.66, 4.55	694
Levetiracetam	139	5	3.6	1.27	0.37, 4.29	289
Topiramate	53	1	1.9	0.66	0.09, 5.96	149
Phenytoin	44	1	2.3	0.80	0.10, 6.61	88
Oxcarbazepine	19	1	5.3	1.85	0.23, 15.04	26
Clonazepam	26	0	0			123
Gabapentin	0	–	–			37
Clobazam	2	0	0			35
Ethosuximide	5	0	0			16
Acetazolamide	1	0	0			3
Phenobarbitone	2	0	0			6
Pregabalin	1	0	0			4
Primidone	2	0	0			8
Tiagabine	1	0	0			6
Vigabatrin	1	0	0			9
Lacosamide	0	–	–			10
Sulthiame	0	–	–			1
Zonisamide	0	–	–			4

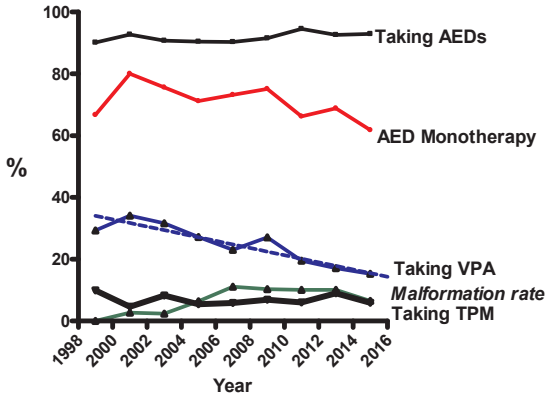

Fig. 3. Changes with time in the proportion of pregnancies exposed to AEDs, and exposed in AED monotherapy, those exposed to valproate (VPA) and topiramate (TPM), and those bearing malformed foetuses.

declined ($P < .05$) and its dosage also fell, (from a mean of 1265 ± s.d. 806 mg/day in 31.1% of all pregnancies in the 1999–2001 triennium to 589 ± s.d. 241 mg/day, in 13.4% of all pregnancies in the 2014–2016 triennium; difference = 676 mg/day, 95% C.I. 360, 992 mg/day). Topiramate had not been prescribed in pregnancies that began before 2000. Its use plateaued by 2006, and declined after 2014.

3.3. Foetal malformations - overall

Logistic regression analysis identified items recorded in the APR database that appeared possibly relevant in relation to foetal malformations (categorised as in the Victorian Birth Defect classification [2]). Items showing statistically significant associations with malformations were (i) a previous malformed foetus, (ii) seizures in a pregnancy before its enrolment in the APR, and (iii) treatment with valproate, carbamazepine or topiramate during the early months of pregnancy. Folate intake before and during pregnancy had no significant association. In relation to pre-conception folate supplementation the malformed pregnancy rate was 5.08% in 1495 pregnancies so treated, and 4.94% in 628 untreated ones (relative risk 1.02;95% C.I. 0.69, 1.55).

3.3.1. Role of a previous malformed foetus

Of the 28 women involved in second or subsequent pregnancies who had malformed foetuses in a previous pregnancy, 7 (25%) had another malformed foetus. In the same situation, but where there had been no previous malformed foetuses, the risk of a malformed foetus was 25 in 376 (6.64%), a relative risk of 3.76 (95% C.I. 1.70, 7.92).

3.3.2. Role of seizures in early pregnancy

No seizure diaries were kept, but seizures were reported to have occurred in the year before pregnancy during 726 of 2121 pregnancies, the remaining 1395 being seizure-free. Malformation-carrying pregnancies occurred in 58 of the first group (8.0%), and in 85 of the second (8.0% *v* 6.1%; R.R. = 1.31; 95% C.I. 0.95, 1.81). Thus active seizure disorders at the outset of pregnancy appeared to have no statistically significant role in contributing to foetal malformation. The corresponding malformation-carrying pregnancy rates for the AED-unexposed pregnancies were 2 in 68 (2.9%) and 3 in 104 (2.9%) – see immediately below.

3.3.3. Role of AEDs

By the end of pregnancy, four of the 176 AED-unexposed pregnancies had yielded malformed foetuses (2.3%), and a further instance was recognised by one-year post-partum (2.8%). Such malformation rates were within the 2%–3% range expected in normal pregnant women. The data for the AED-unexposed pregnancies had been collected in the same manner as that for the AED-exposed pregnancies, their demographical detail (provided above) did not differ and both groups were comprised almost exclusively of women with epilepsy. Therefore the AED unexposed pregnancies were used as an internal comparison population in assessing relationships between intrauterine AED exposure and foetal malformations. As already mentioned, malformation-carrying pregnancy rates at the end of the post-partum year were expressed relative to the number of pregnancies with known outcomes by the end of pregnancy. Consequently, the unavailability of complete data by the one-year post-partum stage may have underestimated the true final malformed pregnancy rates.

By the end of pregnancy, foetal malformations were identified in 105 of the 1972 AED-exposed pregnancies (5.3%). An additional 35 malformation-affected pregnancies were recognised by the end of the postpartum year (final rate = 7.1%), a statistically significantly higher value than the 2.8% rate in the AED-unexposed pregnancies (R.R. = 2.60; 95% C.I 1.08, 6.27). By four months postpartum, 53% of the delayed-recognition malformed pregnancies had been detected and 91% by six months.

Final malformation-carrying pregnancy rates associated with individual AEDs, when used in monotherapy, are shown in Table 1. Only the rate associated with valproate statistically significantly exceeded that for the AED-unexposed pregnancies. At valproate doses of 600 mg/day and below, the malformation hazard ratio was increased (2.11; 95% CI. 0.66, 6.11) and became statistically significantly so by doses of 700 mg/day (3.11; 95% CI. 1.30, 10.22). The rates for the individual drugs employed in monotherapy plus polytherapy are not shown in the Table, because the teratogenic contributions from the individual AEDs in combination cannot be determined, though multivariate logistic regression analysis can throw light on the matter.

Even at the lowest commonly used valproate dose (400 mg/day) the risk of malformation-associated pregnancy was increased (4 in 35 *versus* 5 in 176 for AED-unexposed pregnancy; R.R. = 4.02; 95% C.I. 1.14, 14.24). The rates for the individual drugs employed in monotherapy plus polytherapy are not shown in the Table, because the teratogenic contributions from the individual AEDs in combination are not known,

Table 2
Coefficients of the slopes for doses of the individual AEDs in logistic regressions of the form: Logit risk = $a + b_1$Dose A + b_2 Dose B + ……b_n Dose N, for (i) the full database (ii) AEDs in monotherapy, and (iii) AEDs in polytherapy. Numbers of pregnancies involved in the full data set, and monotherapy equations are those indicated in Table 1, with the numbers for the polytherapy equations being obtained by difference.

	Full Data Set			Monotherapy only			Polytherapy only		
AED		Slope	P		Slope	P		Slope	P
VPA	+	0.000985	< **.0001**	+	0.001207	< **.0001**	+	0.000461	.0741
CBZ	+	0.000192	.4604	+	0.000559	.1454	–	0.000592	.1813
LTG	–	0.000951	.1522	–	0.000040	.9671	–	0.002705	**.0220**
LEV	–	0.04893	.4240	–	0.081439	.4661	+	0.000061	.7030
TPM	+	0.002517	**.0105**	–	0.003665	.4619	+	0.002753	**.0158**
PHT	–	0.018046	.7585	–	0.273858	.4146	–	0.001381	.4966
CZP	+	0.021509	.6707	–	53.853649	.9972	+	0.006398	.8993
GPT	–	0.048186	.9909	+	0.046873	.9978	–	0.051177	.9929
OXC	+	0.000583	.3714	+	0.000763	.3284	–	0.000497	.7155
CBM	–	0.005763	.8488	+	0.016001	.7054	–	0.026399	.5431

though multivariate regression analysis can throw light on the matter.

Multiple variable logistic regressions were calculated for the risk of malformation-carrying pregnancy on doses of individual AEDs in (i) the overall data, and in (ii) monotherapy and (iii) polytherapy (Table 2). The partial correlation coefficient values for the equations for the various AEDs are derived from the corresponding number of pregnancies shown in Table1.

In the full data set there were statistically significant relationships between increasing doses of valproate and topiramate and increasing risk of malformation-carrying pregnancy. This increased hazard also applied for valproate in monotherapy, and for topiramate in polytherapy. No combination between topiramate and any other AED appeared to be particularly associated with teratogenesis. There were 2 instances in 31 combinations involving carbamazepine, 2 in 32 combinations involving lamotrigine, 2 in 27 involving levetiracetam, 2 in 25 including valproate and 2 in 14 involving clonazepam. No AED other than those mentioned in the immediately preceding sentence was involved in more than 5 combinations with topiramate. In polytherapy, increasing lamotrigine dosage was associated with a decreasing chance of malformation-carrying pregnancy. Rates of occurrence of pregnancies carrying malformed foetuses are plotted against drug dosage for valproate and topiramate in Fig. 4.

3.3.4. AED polytherapy per se

Malformation-carrying pregnancy rates reported in the literature have usually been higher in association with AED polytherapy than monotherapy. This was the case in the present analysis (8.1% in 555 polytherapy pregnancies *versus* 6.3% in 1593 monotherapy ones: R.R. = 1.29, 95% C.I. 0.87, 1.82). However, an earlier analysis of a smaller set of the APR data had found a lower rate in the polytherapy group [3]. Excluding all pregnancies involving valproate in the present analysis changed the rates to 7.3% in 344 pregnancies, and 4.6% in 1127 pregnancies respectively (R.R. = 1.58; 95% C.I. 0.99, 2.50), then excluding all additional pregnancies involving topiramate exposure yielded quite similar malformation-carrying pregnancy rates, viz.4.4% in 270 and 4.7% in the remaining 1074 pregnancies. Rather than being a consequence of polytherapy *per se,* the presence of either valproate or topiramate in AED polytherapy seems to account for the higher malformation-carrying pregnancy rate observed in association with AED polytherapy, the malformation risk with the exclusions falling from 8.1% to 4.4% (Odds Ratio 0.53; 95% C.I. 0.27, 1.01).

3.3.5. Specific malformations

An earlier study of APR data found relationships between some more common individual foetal malformations and intrauterine exposure to particular AEDs [4]. At that time there were statistically significant associations between valproate and spina bifida, malformations of the heart, digits, skull bones and brain; between topiramate and hypospadias and brain malformations; and between carbamazepine and urinary tract malformations. Over the years surveyed there was a decreasing incidence of spina bifida and hypospadias as valproate use and dosage had fallen [5]. This may explain why logistic regression analysis of the present larger APR data set, relating the risk of malformation of particular foetal anatomical parts to individual AED dosage in monotherapy, found statistically significant associations only between spina bifida and valproate, malformations of the heart and lamotrigine, and malformations of the urinary tract and carbamazepine (Table 3).

3.3.6. Implications of stage of pregnancy at APR enrolment

Could rates of malformation-bearing pregnancy in the current analysis have been influenced by women enrolling in pregnancy after they already knew whether their foetuses were normal?

The rates of malformation-carrying pregnancy detected at birth were: enrolled in the first 90 days of pregnancy 3.8% in 368 pregnancies; in the second 90 days 4.3% of 941 pregnancies, and in the final 90

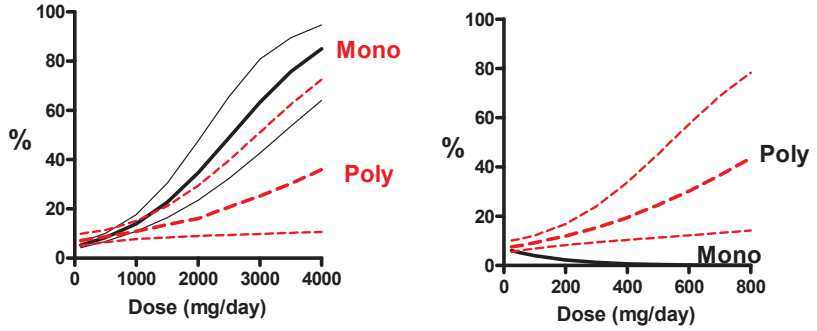

Fig. 4. Logistic regressions for foetal malformation rates and their 95% confidence intervals for valproate in monotherapy and polytherapy (left panel) and for topiramate in monotherapy and polytherapy (right panel), on drug dosage. Polytherapy data are shown as broken lines.

Table 3
Logistic regression partial correlation coefficients and their P values for the risk of particular foetal malformations, and malformation affected anatomical body systems, on daily doses (mg/day) for the more frequently used AEDS.

Malformation	VPA	CBZ	LTG	LEV	TPM	PHT	CZP
Spina bifida	**+0.0010**	+0.0013	−0.0042	−0.0200	−0.0018	−0.0913	−916.96
	P < 0.01	P = 0.189	P = 0.457	P = 0.999	P = 0.824	P = 0.999	P = 0.998
Heart	−0.0003	−0.0004	**+0.0031**	+0.0001	−0.0015	−0.0056	+0.7517
	P = 0.367	P = 0.510	**P = 0.044**	P = 0.781	P = 0.544	P = 0.424	P = 0.200
Hypospadias	+0.0003	−0.0002	−0.0003	+0.0001	+0.0030	0.0036	+0.7201
	P = 0.208	P = 0.768	P = 0.246	P = 0.865	P=0.162	P = 0.450	P = 0.376
Face/mouth	−0.0000	+0.0000	−0.0024	−0.0197	+0.0013	−0.0956	−903.98
	P = 0.951	P = 0.970	P = 0.490	P = 0.999	P = 0.720	P = 0.999	P = 0.996
Skull bones	+0.0000	+0.0006	+0.0016	−0.0001	−0.0095	+0.0057	−6.2305
	P = 0.973	P = 0.418	P = 0.431	P = 0.893	P = 0.344	P = 0.320	P = 0.648
Digits	+0.0003	−0.0009	−0.0067	−0.0008	−0.3629	−0.0906	−981.94
	P = 0.317	P = 0.306	P = 0.099	P = 0.325	P = 0.999	P = 0.999	P = 0.996
Urinary tract	−0.0012	**+0.0019**	+0.0017	+0.0003	+0.0036	−0.0986	−800.85
	P = 0.385	**P = 0.049**	P = 0.539	P = 0.559	P = 0.179	P = 0.999	P = 0.997

days 5.7% in 563 pregnancies. For pregnancies in which foetal malformations were not notified until the one-year postpartum interview, the corresponding figures were 0.82%, 0.85% and 0.89%. Such numbers are too small to permit unambiguous conclusions, the higher risk for malformations recognised by birth for the last *versus* the first 90 days enrolment stages not being statistically significant (R.R. = 1.49, 95% C.I. 0.81, 2.76).

4. Discussion

The current medical literature contains a number of analyses of the association between antiepileptic drug exposure during pregnancy and foetal malformation. Overall, there is general agreement between most of these studies, particularly the more recent ones, but the numerical values for the rates of occurrence of malformation-carrying pregnancy vary. This variation probably depends on the natures of the population studied, the doses of the antiepileptic drugs involved, and probably other factors. To facilitate comparisons between studies, and to assist possible future meta-analyses, a present account provides a reasonable amount of information concerning the APR's recruitment policies, composition and approach to data analysis.

There have been differences between the populations used as a basis of comparison with the antiepileptic drug treated pregnancies in the literature. Arguably, the ideal comparator would be the pregnancies of women with AED-untreated epilepsy of similar type and severity to that in the population investigated, and whose data were collected in the same way as that of the AED-exposed pregnancies. An approximation to such a set was used in the present study, but such pregnancies were difficult to recruit, and their relatively small numbers reduce the statistical power of the study. The data for these AED-unexposed pregnancies had been collected in the same manner as that for the AED-exposed pregnancies, their demographical detail provided above did not differ and both groups were comprised almost exclusively of women with epilepsy. Other studies have used comparators such as previous AED-unexposed pregnancies in the same women, matched pregnancies in non-epileptic women, pregnancies from the same data set of women but with epilepsy treated with an AED believed to have a low or negligible teratogenicity potential, or whole population data for pregnant women in a particular region or country where such information is collected by official agencies.

Ideally malformation rates would be derived after following pregnancies prospectively from the moment of conception, but this is nearly always impracticable. The later the stage at which a pregnancy is enrolled voluntarily into a database dealing with foetal malformations, the greater the chance of bias because knowledge of whether or not the foetus involved is normal, and pregnancies carrying malformed foetuses being aborted and escaping recording. An attempt was made to evaluate these possibilities in the present study. There were higher foetal abnormality rates in late-enrolled as compared with early-enrolled pregnancies, but the differences were not statistically significant. Nevertheless, the possibility of selective inclusion of pregnancies that carry malformed foetuses cannot be excluded.

In the literature foetal malformation rates have been determined at different stages, *e.g.* at the end of the post-natal month or 3 months, and sometimes expressed relative to numbers of pregnancies or of live births. The present study used malformation-carrying pregnancy rates at the end of the post-partum year that were expressed relative to the number of pregnancies with known outcomes by the end of pregnancy. This may account for differences between rates in the present paper and other communications in the literature. Further, the unavailability of complete data by the one-year post-partum stage because of failure to trace some women may have tended to underestimate what would have been the true final malformed pregnancy rates.

The present study has other limitations resulting from various factors, *e.g.* the inability to personally manage the pregnancies concerned and the reliability of information that is ultimately derived from lay sources, even if provided through professional informants. However, such limitations usually beset population data collections, and simply have to be accepted in attempting to draw conclusions from such material.

The main findings of significance that have emerged from analyses of the APR have been in relation to the teratogenicity of valproate, topiramate and less certainly carbamazepine, the probable foetal safety of levetiracetam, lamotrigine and clonazepam (though with relatively small numbers for the use of the latter in monotherapy), and the refutation of the earlier belief that antiepileptic drug polytherapy *per se* increased the teratogenicity hazard. A greater incidence of malformed foetuses-carrying pregnancies in AED-treated women provides evidence of teratogenicity from these drugs, but the evidence is strengthened if the incidence of the malformation-carrying pregnancies increases with increasing dosage of the drug involved.

Such a dose-related malformation hazard was recognised in relation to valproate in the earliest analyses of the APR data. Initially, valproate doses below 1100 mg a day [6] or 1400 mg a day [7] seemed safe for the foetus. However, with data accumulation, it became clear that the hazard increased progressively with increasing valproate dosage. Enough evidence from other sources has appeared in the literature to put the teratogenicity of valproate beyond reasonable doubt. Awareness of this has led to reduced usage and dosage of the drug in pregnant women, and in those who may become pregnant.

As early as 2008, Hunt et al [8] provided statistically significant evidence of teratogenicity from topiramate. The APR did not detect this hazard until 2014 when a regression analysis detected dose-related teratogenicity of the drug [9]. At that time the previously declining rate

of malformation-carrying pregnancies in the APR as valproate use decreased appeared to become reversed. This reversal coincided with increasing use in pregnancy of newer AEDs (topiramate, lamotrigine, levetiracetam) [10,11]. There was evidence, confirmed in the present analysis, that lamotrigine and levetiracetam were not responsible for the reversal and that topiramate probably was [12]. Both in the APR data, and in the report of Keri et al [13], topiramate teratogenicity appears related to the drug's use in AED polytherapy. It is unclear whether the difference in malformation hazard between topiramate monotherapy and polytherapy is related to lower doses of the drug and use in smaller numbers of women in monotherapy, or whether some interaction between topiramate and co-administered AEDs has produced a teratogenic derivative.

Among the other more commonly used AEDs that were studied, carbamazepine seems associated with the strongest suspicion of a teratogenicity hazard. Publications in the literature have usually shown increased malformation relative risks for the drug, though in only one [14], and in meta-analyses was the increase statistically significant [15–17]. In the present analysis there was a statistically significant association between carbamazepine exposure and developmental abnormalities in the foetal urinary tract. It seems that carbamazepine probably possesses some teratogenic capacity, but not to the extent that valproate and topiramate do.

In both the APR data, and in the available literature, the increasingly widely used lamotrigine and levetiracetam appear safe from the foetal structural development point of view.

The literature has sometimes suggested that AED combinations, as a class, are associated with a greater hazard the foetal malformation than AED monotherapy (*e.g.* [18–20]). However, analysis of the APR's data [3], and two almost simultaneous studies [21,22] suggested that no class effect is involved, but simply consequences of the presence of teratogenic agents (valproate or topiramate) in some AED combinations. The present analysis of the APR data provides no reason to revise this conclusion.

The association found in the present analysis between previous pregnancies where there has been a foetal malformation and current malformation-carrying pregnancy, was noted earlier [23]. It raises the possibility that genetic factors may play a role of AED -related foetal malformation.

5. Conclusion

The present analysis has shown that the conclusions regarding foetal malformations derived from earlier analyses of smaller data sets from the APR have remained valid. Enough material regarding the older well-established AEDs is currently available in the APR to permit conclusions that appear trustworthy. Some of these conclusions, particularly that in relation to valproate, have already altered clinical practice, and the data that have become available may lead to caution in the use of topiramate. It seems unlikely that analysis of larger data collections in the APR will produce new insights regarding these older drugs and foetal malformation overall, though it may detect relationships between particular drugs and specific malformations.

We may now be at a stage where some time may need to pass before the APR can accumulate sufficient material on the AEDs currently beginning to come into clinical use in pregnant women before analysis of the database can throw much further light on the matter of AED-associated teratogenicity [24]. More information concerning the possible hazards of particular AED combinations would be desirable, as would be the ability to follow pregnancies from before conception, despite the practical difficulties.

Disclosure of conflict of interest

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