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Pregnancies in women with epilepsy

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ABSTRACT The aim of this study was to analyse the outcomes of all the pregnancies of each woman with epilepsy in the Australia Pregnancy Register. Data from 1,290 pregnancies in 612 women with epilepsy were analysed, including 156 women who took no AEDs in the first trimester of at least one pregnancy. Spontaneous miscarriages were more frequent in AED-exposed pregnancies. There was an overall 13·95% risk of a woman taking AEDs during pregnancy having a malformed foetus at some stage of her reproductive career, at least to the time of the present analysis. This risk increased with (i) first trimester exposure to VPA, particularly in maternal doses above 1,100–1,400 mg per day, (ii) the number of pregnancies a woman underwent, although the individual pregnancy risk did not increase from one pregnancy to the next, (iii) history of a previous foetus with a malformation from an AED-associated pregnancy, (iv) twin pregnancies, and (v) family histories of foetal malformations. These findings provide a basis for advising women with epilepsy about the likely overall outcomes of their child-bearing careers, and suggest that both genetic and drug-related factors operate in producing foetal malformations. The issue is one of frequent concern and discussion with participants in the Pregnancy Register.

KEYWORDS Antiepileptic drugs, epilepsy, foetal malformations, miscarriage, repeated or serial pregnancies, twins

LIST OF ABBREVIATIONS Antiepileptic drug (AED), valproate (VPA), confidence interval (CI), odds ratio (OR)

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INTRODUCTION

The woman with epilepsy who has recently become pregnant, or is planning pregnancy, is often concerned about the outcome for her unborn child, especially if she is being treated with AEDs. She may also be concerned about the prospects for her future pregnancies. A good deal of information is available concerning the outlook for each individual pregnancy in a woman taking AEDs. In these circumstances the overall risk of foetal malformation appears to be increased two-fold or three-fold.[1,2] This information has been obtained from analyses of data collections primarily concerned with the course and outcome of individual pregnancies in women with epilepsy. However, some data collections appear to involve material from more than one pregnancy in the same woman.[3–7] Nonetheless, there is not nearly as much information available concerning the outcomes for all the pregnancies that a given woman with epilepsy may undergo as there is for each individual pregnancy. The present paper attempts to address this deficiency in knowledge. It analyses all the pregnancies undergone by each individual epileptic woman, relating the maternal and foetal outcomes to various possibly relevant factors.

As information in the Australian Register of Antiepileptic Drugs in Pregnancy has expanded with the passage of time, its data have been analysed on several occasions, always in terms of the situation for the individual pregnancy.[8–10] In this Register the names of pregnant women have been removed to ensure privacy, and only code numbers have been employed for identification. Utilising the code numbers, it is possible to link the individual pregnancy data to the names of the pregnant women, which are held in a separate database. This linkage permits an analysis of the material up to May 2005, which in this paper has been considered principally from the standpoint of all the pregnancies of each individual woman rather than from the standpoint of each of her pregnancies separately. Such an analysis might throw light on the overall child-bearing outcomes for AED-treated women with epilepsy, and be of assistance to those attempting to provide informed advice to women with epilepsy considering their overall reproductive careers.

MATERIALS AND METHODS

The data of this paper were drawn from the Australian Register of Antiepileptic Drugs in Pregnancy, based in

Melbourne, originally at St Vincent's Hospital and subsequently at Monash University. Information about the existence of the Register and its contact details was given to pregnant women with epilepsy by their treating medical practitioners, and by various lay organisations, and was also made available to other women taking AEDs for non-epileptic indications. Thereafter, contact with the Register was left to the discretion of the women concerned. In the Register, data concerning the present pregnancy and any previous pregnancies were recorded in a computerised database and, with permission from the woman involved, certain medical details were obtained from treating medical practitioners. All contact with the Register was by telephone since the distances between the Register site and the domiciles of many of the pregnant women made any other form of contact impracticable. Details of the current pregnancy were included in the Register on four occasions, namely at recruitment (usually in early pregnancy), at approximately seven months of pregnancy, within one month after giving birth and, finally, one year later. At the initial interview, information was also sought concerning all the woman's previous pregnancies. The women's contact details were kept in a separate database, the only linkage mechanism between the two databases being an identification number. The project was under the oversight of the relevant institutional ethics committees.

For this paper, the data were analysed in relation to all pregnancies of each individual woman involved. It was sometimes also desirable to analyse the data in relation to individual pregnancies, since some women took different AEDs in different pregnancies, or took no AEDs in some pregnancies.

Previous analyses of the Register data had shown that pregnancies exposed to VPA alone or together with other AEDs, had a significantly greater, and also dose-dependent, risk of resulting in a malformed foetus than pregnancies involving exposure to other AEDs.[10, 11] Therefore in the present study, women with pregnancies exposed to VPA were analysed as a separate sub-group within the overall population of women with AED-exposed pregnancies.

RESULTS

The Australian Register, as of May 2005, contained details of 612 women with epilepsy, all of whose pregnancies had known outcomes. These women had undergone a total of 1,290 pregnancies, 637 of which either were current or had begun after recruitment into the database. The 612 women had also experienced 653 pre-recruitment pregnancies, for which data were entered into the database. Of the 612 women, 253 had undergone only one pregnancy. In at least the first trimester of pregnancy 156 of the women had taken no AEDs in a total of 203 pregnancies. The drug-free pregnancies were mainly first pregnancies. All but 60 of these 156 women took AEDs throughout their subsequent pregnancies. Each of the 60 women who were not treated with AEDs in the first trimester of any pregnancy had undergone only one pregnancy by the time of the present data analysis.

There were 196 women who had taken VPA alone, or together with other AEDs, in a total of 350 pregnancies, 356 women who had taken other AEDs but never VPA, and 60 women who had taken no AEDs in at least the first trimester of any pregnancy. Valproate doses were not recorded for pregnancies completed prior to recruitment into the Register, so that VPA dosage data were available for only 149 of the 196 women exposed to the drug.

The 1,290 pregnancies resulted in six stillbirths, six abortions carried out for *in utero* foetal death, 65 pregnancy terminations for various maternal indications, 27 abortions for antenatally recognised foetal malformations (also included in the total of foetal malformations), 186 spontaneous miscarriages, and 1,000 live births.

Spontaneous miscarriage

One or more spontaneous miscarriages occurred in 127 of the 612 women (20·75%), there being a total of 186 miscarriages. Of these 186 miscarriages, 17 (8·38%) occurred in the 203 pregnancies not exposed to AEDs in at least their first trimester, and 169 (15·55%) in the 1,087 AED-exposed pregnancies. The difference in miscarriage rates was statistically significant (OR=0·496; 95% CI=0·294 to 0·838). Miscarriage rates were very similar in the 350 pregnancies exposed to VPA (15·43%) and in those exposed to AEDs other than VPA (15·60%).

Adequate data to assess the possible role of seizure control in relation to miscarriages were available only for pregnancies that had not been completed before women were recruited into the Register. By the initial interview during pregnancy, seizures were not controlled in 12 of 23 pregnancies that resulted in spontaneous miscarriage (52·2%), and in 237 of 655 (36·2%) where no spontaneous miscarriage occurred (OR=1·92; 95% CI=0·836 to 4·48). Convulsive seizures had occurred in 3 of the 23 pregnancies that miscarried (13·0%) and in 97 of 655 (14·8%) that had not miscarried (OR=0·863; 95% CI=0·252 to 2·96). Because the initial interview had not taken place at the same stage of all pregnancies, similar calculations were carried out for the intervals between the initial and the seven-month interviews. Over this interval, seizure control was absent in 3 of 23 pregnancies that miscarried (13·0%) and in 162 of 655 (24·7%) that did not miscarry (OR=0·456; 95% CI=0·134 to 1·56). For the occurrence of convulsive seizures the corresponding figures were 1 in 23 (4·4%) and 67 in 655 (10·2%), with an OR of 0·399 (95% CI=0·53 to 3·01). Thus uncontrolled epileptic seizures seemed unlikely to explain the higher incidence of spontaneous miscarriage in women taking AEDs.

TABLE 1 Malformation rates in the different pregnancies of individual women with epilepsy taking AEDs.

Pregnancy Number	Taking VPA (N=350)	Rate %	Taking other AEDs (N=737)	Rate %	Taking any AEDs (N=1,087)	Rate %
1	24 / 185	12·97	18 / 365	4·93	42 /550	7·64
2	10 / 89	1·24	12 /204	5·88	22 / 293	7·51
3	6 / 46	13·04	2 / 102	1·96	8 / 148	5·41
4	5 / 23	21·74	4 / 43	9·30	9 / 66	13·64
5	0 / 5	0	2 / 18	11·11	2 / 23	8·69
6	0 / 2	0	0 / 4	0	0 / 6	0

In AED-treated women with epilepsy, the miscarriage rates in the first, second, third, fourth and fifth drug-exposed pregnancies were, respectively, 12·7, 18·4, 22·3, 13·6 and 13·0%, and in the drug-untreated women 8·0%, 11·4% and 7·7% in their first three pregnancies, respectively. There appeared to be no systematic tendency for miscarriage risk to change progressively as the number of the pregnancy in the individual woman increased.

Foetal malformations

There were 90 pregnancies that resulted in foetal malformations categorisable according to the Victorian Classification of Birth Defects.[12] Foetal malformations that were recognised at any stage up to one year postnatally, including pregnancies aborted because such malformations had been detected prenatally, occurred in seven (3·45%) of the 203 pregnancies not exposed to AEDs in at least their first trimester. Malformations occurred a little more than twice as often in the 1,087 drug exposed- pregnancies (in 83, ie. 7·64 %: OR=2·01; 95% CI=1·19 to 3·40). The malformation rate, 45 in 350 VPA-exposed pregnancies (12·86%), was statistically significantly higher than the rate that in pregnancies exposed only to other AEDs (38 in 737, 5·15%; OR=2·71; 95% CI=1·73 to 4·27). The malformation rate in pregnancies not exposed to VPA (5·15%) was not statistically significantly different from the 3·45% rate in pregnancies not exposed to AEDs (OR=1·52; 95% CI=0·669 to 3·46). Malformation rates were reasonably similar in all pregnancies exposed to AED monotherapy (7·03%) and polytherapy (6·45%); difference=0·58%; 95% CI=-2·9% to 4·0%.

Table 1 relates the rate of occurrence of pregnancies resulting in foetal malformation to the number of the AED-exposed pregnancy in the individual woman (including pregnancies resulting in spontaneous miscarriage). The rates of malformation-associated pregnancy seem relatively constant irrespective of the number of the pregnancy. Linear regression analysis showed no statistically significant trend with the number of the AED-exposed pregnancy. The risk of pregnancy resulting in foetal malformation appeared independent of the number of the pregnancy in the individual woman.

Differences in overall malformation rates between earlier and later pregnancies in the same woman could have been caused by increasing awareness of the greater teratogenic potential of VPA resulting in decreased use of the drug as time passed. Of 269 women in the data collection who received AEDs in their penultimate pregnancy, 86 were taking VPA; in the same population in their final pregnancies, 16 were no longer taking VPA, but 14 previously unexposed to the drug had been prescribed it, so that there remained a total of 84 who took the drug. Of 12 women whose penultimate pregnancy whilst taking VPA had resulted in a foetal malformation, nine continued to take the drug in their final pregnancies.

The 90 pregnancies that resulted in malformed outcomes occurred in 79 women with epilepsy. During the reproductive careers of the 612 women with epilepsy, to the stages reached by the time of the present analysis of data, an individual epileptic woman had a 12·85 % overall chance of a pregnancy which resulted in a foetal malformation. Excluding the 60 women who had never been exposed to AEDs in the first trimester of any of their pregnancies (by the time of the present analysis), the risk for an AED-treated epileptic woman having a pregnancy that resulted in a foetal malformation was 77 in 552 (13·95 %). To the time of the present analysis, the risk for having a malformation-associated pregnancy at some stage in their reproductive careers was 9·14% in 361 women exposed only to AEDs apart from VPA, but 22·96% in 196 women who had pregnancies exposed to VPA (OR=0·338: 95% CI=0·207 to 0·555).

A logistic regression was calculated for the risk of malformation-associated pregnancy on drug dose for the 149 women who took VPA in known dosage in the first trimester of pregnancy (see Figure 1). For the purposes of this regression, if a woman had taken the drug in different doses in different pregnancies, only the data for the highest dose were used: if the drug was taken in the same dose in all pregnancies, the data for the earliest pregnancy were used. From the shape of the regression curve, it appeared that the risk of malformation-associated pregnancy began to increase more steeply when a VPA dose of 1,100–1,400 mg per day was exceeded. Above a dose of 1,400 mg per day, 14 of 49 women (34·15%) had undergone one or more

TABLE 2 Cumulative risk of a woman undergoing a malformation-associated pregnancy related to the number of pregnancies undergone in 293 women who had taken AEDs in one or more pregnancies. Some women had taken VPA in some pregnancies, but not in others, so that the numbers of women in the different columns do not always reconcile.

Numbers of Pregnancies	Any AED		VPA		Non-VPA drugs	
	Malformed	%	Malformed	%	Malformed	%
1	14 / 151	9·27	6 /49	12·24	8 /100	8·00
2	24 / 151	15·89	10 / 49	20·41	14 / 100	14·00
3	13 / 83	15·66	5 /22	22·73	8 /61	13·11
4	16 /43	37·21	8 /18	44·44	8 /25	32·00
5	8 /17	47·06	3 /3	100·00	5 /14	35·71
6	1 /6	16·67	1 /2	50·00	0 /4	0

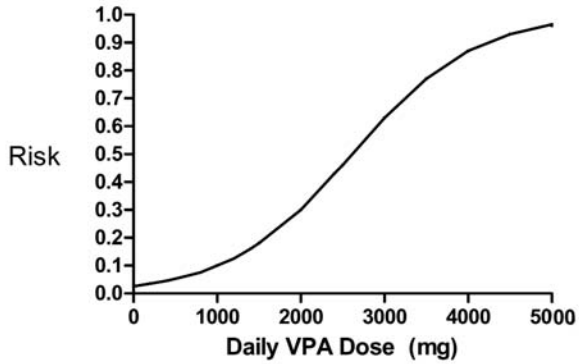

FIGURE 1 Logistic regression relating the risk of a woman with epilepsy having at least one malformation-associated pregnancy to the dose of sodium VPA taken in the first trimester of pregnancy. The regression equation is: logit Risk = -3·5698 + 0·00137 Dose (P<0·0001).

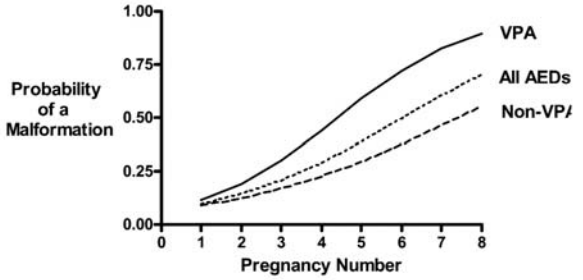

FIGURE 2 Logistic regression for the probability of having a malformation-associated pregnancy on the number of the pregnancy in an AED-treated woman. For all AED-exposed pregnancies the regression equation is: logit risk = -2·6555 + 0·4397 number of the pregnancy (P<0·0001); for women with VPA exposed pregnancies: logit risk = -2·6279 + 0·5988 number of the pregnancy (P = 0·0005); for women exposed to AEDs apart from VPA: logit risk = -2·6750 + 0·3608 number of the pregnancy (P=0·0004).

malformation-associated pregnancies; below this dose 6 of 108 (5·55%) had undergone such pregnancies (OR=8·81; 95% CI=3·31 to 25·1).

Ten of the women with epilepsy in the Register had undergone more than one malformation-associated pregnancy, one having three such pregnancies. The Register contained a total of 293 women who were at risk of having foetal malformations in more than one pregnancy. Of these 293 women, 49 had at least one malformation-associated pregnancy before their final pregnancy that was included in the Register. Foetal malformation occurred in the final pregnancy in 10 of these 49 women (20·41%). Of 244 women who had no previous malformation-associated pregnancies prior to their final one in the Register, 13 (5·33%) had a malformation-associated final pregnancy. The risk of the final pregnancy being a malformation-associated one was statistically significantly higher in the women who had already experienced one or more previous pregnancies associated with foetal malformations than in those who had not (OR=4·56; 95% CI=1·87 to 11·1). The 49 women with malformation-associated pregnancies prior to their final pregnancy had undergone a mean of 2·39 pregnancies, and the 252 women with no malformation-associated pregnancies before their final pregnancy had a mean of 2·72 pregnancies. Therefore the higher rate of malformation-associated pregnancies in the women with previous pregnancies that had yielded malformed offspring was unlikely to be simply due to these women having undergone more pregnancies.

Previous pregnancies that resulted in foetal malformations occurred in 24 women who took VPA in their final pregnancies. Of these 24, five (20·8%) had malformed foetuses in their final pregnancies. Of 101 women whose previous pregnancies had not resulted in foetal malformations and who took VPA in their final pregnancies, nine (8·9%) had a malformed foetus in their final pregnancy (OR=2·69; 95% CI=0·811 to 8·93). This difference is not statistically significant but points in the direction of a genetic factor contributing to the repeated occurrence of malformations. Insufficient data were recorded concerning the fathers involved to obtain any

indication as to whether the postulated genetic factor was maternal, or paternal. Pursuing the matter further in relation to biological fathers may have raised unacceptable issues and impaired recruitment into the Register.

Table 2 shows the cumulative risk, as the number of pregnancies undergone increased, of having a malformation-associated pregnancy for a woman in the Register who took AEDs in more than one pregnancy, and also the risk for the woman who took VPA in all her pregnancies, and the risk for the AED-treated woman who had never taken VPA. The risk appeared to increase with increasing numbers of pregnancies in the individual.

Based on the data of Table 2, logistic regressions (see Figure 2) were calculated for the risk of a malformation-associated pregnancy on the number of the pregnancy in the individual epileptic woman. In women taking AEDs other than VPA the risk of having a malformed foetus reached 50% between the seventh and eighth pregnancy undergone. In women taking VPA the 50% risk was reached between the fourth and fifth pregnancy undergone. There were too few data to determine the corresponding value for women taking higher dosages of VPA.

Family history

There were family histories of foetal malformations in the first and second-degree relatives of 33 of the 79 women in the Register with malformation-associated pregnancies, but in only 46 of the 533 women taking AEDs but without foetal malformation-associated pregnancies (41·77% vs 8·63%: OR=7·59; 95% CI=4·43 to 13·0).

Twin pregnancy

The presence of a twin pregnancy was recorded only for post-recruitment pregnancies. Of 552 first trimester AED-exposed pregnant women, 15 had a total of 16 twin pregnancies. In these 15 women, one or both twins were malformed in four pregnancies (26·67%), as compared with the occurrence of malformation-associated pregnancies in 30 women (5·59%) out of the remaining 537 women (OR=5·31; 95% CI=2·03 to 13·9). There were six malformed foetuses among the 32 twin ones (18·75%), and 41 among the 655 AED-exposed singleton pregnancies (6·26%: OR=6·26; 95% CI=1·37 to 9·01). Exposure to VPA had occurred in 12 of the 32 twin foetuses (37·5%), and in 207 of the 655 singleton ones (31·6%; OR=1·30; 95% CI=0·623 to 2·71). It was unlikely that the increased risk of malformation in twin pregnancies could be accounted for by the more frequent occurrence of exposure to VPA.

DISCUSSION

The data for this paper had been collected primarily from the standpoint of the individual pregnancy rather than that of all the pregnancies that each individual epileptic woman had undergone. This resulted in several limitations to the findings. The pregnancies that were analysed had all been completed, but the full reproductive lives of the women probably were not necessarily completed at the time of the data analysis. Therefore some of the results may underestimate the final situation, though trends that are already apparent seem likely to hold. Deferring publication until all the women involved reached the ends of their reproductive lives would have made the findings of the investigation unavailable for many years. The paper is also based on data that were volunteered by what was almost certainly only a minority of the Australian women with epilepsy (probably about one in seven) who were pregnant during the period of data collection. The women in the Register may not necessarily be representative of the broader population of Australian pregnant women with epilepsy. Those women included were often likely to have become aware of the existence of the Register through contact with particular classes of medical practitioners, especially neurologists. Further, part of the information analysed was obtained months or years after the events recorded had occurred. Its accuracy therefore depended on patients' memories of earlier events. Nevertheless, the use of this retrospective data expanded the comparator group of AED-free pregnancies, though not the number of drug-free women. It also had the advantage that one pregnancy in a given woman sometimes served as a control for another pregnancy in the same woman.

When the database was originally established it was not appreciated that the AED doses taken in previous pregnancies, or the birth of twins, could prove of future interest. Therefore the relevant information concerning these particular aspects was not recorded. The present analysis, being centred principally on the women rather than on each of their individual pregnancies, also encountered the difficulty that some women took different AEDs in different pregnancies, and in some pregnancies may have taken none. All these limitations have been kept in mind in analysing the available data. Nonetheless, by focusing the analysis mainly on the individual woman and her pregnancies rather than on the individual pregnancy it has produced some findings that do not seem to have emerged in the previous literature.

The greater incidence of foetal malformations in AED-exposed pregnancies, particularly those in which VPA was involved (and where the malformation risk increased with drug dosage), had been observed previously in analyses of the same database at earlier stages in its collection.[9–11] This association of foetal hazard with VPA-exposed pregnancy has also been noted by others[7,13,14] and requires little further comment. Nonetheless, the considerably increased hazard of having at least one malformation-associated pregnancy for a woman taking higher VPA doses, illustrated in Figure 1, needs to be kept in mind.

Several previous studies,[15,16] though not all,[17–19] have found a higher incidence of spontaneous miscarriage in the AED-exposed pregnancies than in the pregnancies of untreated women with epilepsy. In the present analysis the increased incidence of spontaneous miscarriages became apparent when the reproductive careers of the individual women were studied. In previous papers based on the Register's data it had not been so obvious when only individual pregnancies were considered. A greater incidence of foetal malformations incompatible with foetal survival was unlikely to explain the increased miscarriage rate associated with exposure to AEDs. If that had been the case the miscarriage rate should have been higher in pregnancies exposed to VPA than in pregnancies exposed only to other AEDs. This was not so. The continuing occurrence of epileptic seizures during pregnancy did not seem capable of explaining the finding, whose basis remains uncertain.

The higher incidence of family histories of foetal malformation in the first and second degree relatives of women who had a malformation-associated pregnancy might suggest that such a family history could provide some indication of the future hazard of foetal malformations in a pregnant woman with epilepsy. However, some women who were aware that they might be carrying foetuses with malformations may have sought out histories of similar events in members of their families before enrolling in the Register, whereas women with normal foetuses may not have. This may have biased some of the data, so that a family history of foetal malformation may not necessarily prove reliable as a guide to the future foetal malformation risk. It does, however, provide support for the proposition that there may be, in at least some women, an underlying genetic predisposition to AED-related birth defects, as suggested previously.[20] There is also evidence from family and twin studies that genetic factors may predispose an individual to having children with AED associated birth defects.[21,22] Animal studies provide support for this.[23] The matter could not be pursued further in the present data.

The risk of undergoing a malformation-associated pregnancy proved relatively constant, irrespective of the number of the individual woman's pregnancy and of her increasing age as her number of pregnancies increased. However, the more pregnancies, including pregnancies that miscarry, that a woman with epilepsy undergoes, the more likely it is that she will have a malformation-associated one. This proved true in the present study. This point does not often seem to be made when advising women with epilepsy at the outset of their reproductive careers. The risk of having a malformed offspring may remain constant from one pregnancy to the next, but the higher this risk of malformation in the individual pregnancy, the fewer pregnancies a woman may undergo before one results in a malformed offspring. This was true of the present data set when the outcomes of pregnancies in women exposed to VPA, with its greater risk of foetal malformation, were compared with the outcomes in women exposed only to other AEDs in pregnancy. There were too few pregnancies in women taking VPA dosages above 1,100–1,400 mg per day to determine the degree of increased hazard in that particular situation. The data of Figure 2, though not based on a particularly extensive dataset, provide some indication of the hazard of a pregnancy resulting in a malformed foetus as the number of pregnancies in the individual woman with treated epilepsy increases.

The growing cumulative probability of having a malformation-associated pregnancy increases as the number of the pregnancy increases in the individual woman. Thus occasional women with epilepsy who undergo several pregnancies may have more than one pregnancy associated with a malformed foetus. The present study showed that a woman who already had a malformation-associated pregnancy ran a greater risk of a further such pregnancy than a woman who had not had a malformation-associated pregnancy. This finding was not simply the consequence of women with previous malformation-associated pregnancies having undergone more pregnancies, and therefore having had more opportunities for pregnancies with malformation, than the comparison group of treated women with epilepsy who had not given birth to malformed offspring. The finding provides further support, along with the family history data, for the existence of a pharmaco-genetic predisposition to AED associated foetal malformations.

The greater risk of having a malformation-associated pregnancy in women who were bearing twins has been found in other studies.[24] Even though only relatively small numbers of women were involved in the present dataset, the finding was statistically significant. It appears to be more than merely a consequence of having twice as many babies per pregnancy. Nonetheless, it would be desirable to confirm it in a larger data set.

The present study provides some information relevant to the longer term outlook for the woman with epilepsy at the outset of her child-bearing career. Her risk of having a single malformation-associated pregnancy, if she is taking AEDs apart from VPA, may not be particularly high. However, she needs to appreciate that the cumulative risk of having at least one pregnancy that results in a foetal malformation increases with each pregnancy she undergoes, even though the risk of malformation in each individual pregnancy remains relatively constant. The risk of foetal malformation is higher if VPA intake is involved, and particularly if the drug must be taken at dosage above 1,100–1,400 mg per day. The absence of any major change in overall VPA usage patterns between pre-final and final pregnancies made it unlikely that altered usage of this particularly teratogenic drug with the passage of time may have confounded the interpretation of the malformation

rates found. The risk of a malformation-associated pregnancy appears higher in twin pregnancies. A further malformation-associated pregnancy also appears more likely if there has been a personal or family history of a previous foetal malformation, consistent with a genetic susceptibility being involved.

The availability of such information, particularly if confirmed in further studies, may assist the woman with epilepsy when taking informed decisions about her future reproductive career.

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