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Abstract

Objective: To clarify whether antiepileptic drug exposure during pregnancy is associated with an increased risk of intrauterine foetal death

Methods: Analysis of data from 2064 pregnancies with known outcomes included in the Australian Register of Antiepileptic Drugs in Pregnancy, 170 of the pregnancies being unexposed to the drugs in at least the first half of pregnancy.

Results: The relative risk (6.46; 95% C.I. 0.90, 46.22) of intrauterine death appeared higher, though not statistically significantly higher, in drug-exposed pregnancies compared with unexposed ones (3.44% v 0.59%). There was no statistically significantly increased hazard associated with AED polytherapy as compared with monotherapy. Logistic regression analysis showed a statistically significantly increased and dose-related hazard of intrauterine death in relation to carbamazepine exposure.

Conclusions: Intrauterine exposure to antiepileptic drugs, particularly carbamazepine, may be associated with an increased risk of foetal death during pregnancy.

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Key Words: Antiepileptic drugs, carbamazepine, foetal death, spontaneous abortion, stillbirth

Introduction

Since 1964 there has been intermittent interest in the question of whether antiepileptic drug (AED) exposure during pregnancy is associated with increased risks of spontaneous abortion or still birth¹. A recent meta-analysis based on 39 relevant studies published between 1990 and 2015 was carried out by Viale *et al*². These authors found that there was a statistically significantly increased hazard of spontaneous abortion but not of stillbirth in the pregnancies of women with epilepsy, as compared with the pregnancies of untreated normal women. The rate of intrauterine foetal death (spontaneous abortion plus stillbirth) was not significantly higher in AED treated pregnancies, but was statistically significantly so in series where over 30% of the pregnancies in the series had been exposed to AEDs, as compared with series with lower rates of pregnancy AED exposure. AED polytherapy was not associated with increased spontaneous abortion or still-birth rates.

The Viale *et al*² paper did not include the recent large study of Tomson *et al*³ that was based on 7055 pregnancies from the EURAP Pregnancy Register. That study found very similar rates of intrauterine foetal death (spontaneous abortion plus stillbirth) for women taking various more commonly employed AEDs (lamotrigine, carbamazepine, valproate, levetiracetam, oxcarbazepine, phenobarbitone) and no correlations with AED dosage. Unfortunately, this study did not include a control group of pregnant women with epilepsy that was not treated with an AED. In contrast to the Vaile *et al*² study, AED polytherapy in the Tomson *et al* study was found to be associated with a statistically significantly higher rate of intrauterine foetal death.

Since the findings of these two studies differed in some regards, we have utilized data from the Australian Register of AEDs in Pregnancy (APR) to investigate the association of AED use during pregnancy with intrauterine foetal deaths. The APR contains a subset of pregnancies unexposed to AEDs, in at least the earlier half of pregnancy, in women with epilepsy, and this subset can provide a comparator for the Register's AED-exposed pregnancies. Data from this work has also been provided for the EURAP dataset in collaboration with the International Register, chaired by T. Tomson.

Material and Methods

Detailed information regarding the APR and its recruitment policies and data handling practices has been published previously^{4,5}. The APR collects details of the pregnancies of Australian women who are taking AEDs, and also those of women with epilepsy that has been untreated in at least the first half of pregnancy. Enrolment in the APR is entirely voluntary and completely at the discretion of pregnant women. The APR is estimated to contain information on about 8.7% of the relevant pregnancies in Australia⁶. All contact with the APR is *via* telephone, with data concerning the course of pregnancy being recorded (i) at enrolment, (ii) at approximately 28 weeks of pregnancy, (iii) within the first post-partum month and (iv) as far as possible, at one year after birth. The accuracy of the information provided by pregnant women is checked with their treating medical practitioners. Throughout pregnancy, the clinical management of the pregnancies enrolled in the APR always remains with the treating medical practitioners, the APR not attempting to influence this management. The APR has been under the ethics oversight of various Melbourne based institutional human ethics committees, with that of the Melbourne Health (The Royal Melbourne Hospital) currently holding the responsibility.

Relevant data from the APR were transferred to an Excel spreadsheet and then analysed by relative risk (R.R.) calculations and logistic regression. Pregnancies ending in spontaneous abortion or in still birth were analysed as a combined category, partly because of the small number of stillbirths, and partly because several pregnancies ended around 28 weeks of gestation, so that their sub-classification into spontaneous abortions or stillbirths was arguable.

Results

To the end of September 2016, after excluding pregnancies lost to follow up, (N = 10) the APR contained contemporaneously collected information on 2064 pregnancies with known outcomes. Of these 66 had resulted in spontaneous abortions, and 7 in stillbirths, i.e. there were 73 unexplained intrauterine deaths after excluding known foetal malformations and therapeutic abortions. No AED exposure had occurred in at least the earlier half of pregnancy in 170 pregnancies, one of which ended in a spontaneous abortion. Women with epilepsy were involved in 97.1% of the AED unexposed pregnancies, and in 98.4% of the AED exposed ones. Of the AED exposed pregnancies, 1367 (including 48 spontaneous abortions

and one still birth) involved a single AED. The remaining 527 AED-exposed pregnancies (including 18 spontaneous abortions and 6 stillbirths) involved exposure to AED polytherapy.

As mentioned above, there was one intrauterine foetal death (at 14 weeks of pregnancy) in the 170 AED-unexposed pregnancies (0.59%) and 72 in the 1894 pregnancies exposed to AEDs throughout in mono- or poly-therapy (3.80%: R.R. = 6.46; 95% C.I. 0.90, 46.22).

However, in the present series the only intrauterine death in the untreated pregnancies occurred in the 14th week of gestation, representing a 3.4% death rate to that time in that subgroup, as compared with a rate of 4.5% in the AED exposed pregnancies in their first 14 weeks. Nonetheless, the different delays in enrolments suggest caution in interpreting findings related to the unexposed pregnancies. This is not an issue in comparisons within the AED exposed pregnancies where carbamazepine is concerned, as here mean delays were very similar.

Monotherapy data: There were 47 intrauterine deaths in the 1367 AED monotherapy pregnancies and one in the 170 AED-unexposed pregnancies (3.44% v 0.59%: R.R. = 5.84; 95% C.I. 0.81, 42.09). Table 1 shows the intrauterine foetal death rates in relation to main individual AEDs used in monotherapy. Only the risk associated with carbamazepine (CBZ) exposure was statistically significantly increased, relative to the AED-unexposed pregnancies (Table 1). The intrauterine death risk associated with carbamazepine exposure was not statistically significantly higher than that associated with all other AEDs in monotherapy (4.70% v 3.12%: R.R. 1.51; 95% C.I. 0.86, 2.65).

It should be noted that the mean interval between the last menstrual period and enrolment in the study was longer in the AED-unexposed pregnancies than in the drug-exposed ones ($23.1 \pm \text{SD } 9.14$ weeks v $20.0 \pm \text{SD } 8.34$ weeks (difference 3.18 weeks, 95% confidence limit 1.65, 4.55). However, the mean delay for carbamazepine monotherapy pregnancies (20.13 weeks) was virtually identical with that for all other monotherapy pregnancies (20.15 weeks).

Polytherapy data

The intrauterine death rate in the 527 AED polytherapy pregnancies was 4.36%, not statistically significantly higher than that in monotherapy pregnancies (3.58%: R.R. 1.22; 95% C.I. 0.75, 1.98).

Other potentially relevant factors

Multivariate logistic regression was used to investigate possible relationships between several variables recorded in the APR database and the risk of intrauterine death in the full 2064 pregnancies, with subsequent serial stripping of variables to obtain an equation of best fit. Use of assisted fertilisation, past histories of stillbirths or births with malformed foetuses, and histories of folic acid use before and during pregnancy, tobacco, alcohol and marijuana use, and occurrence of any type of seizure during pregnancy were eliminated before the following statistically significant regression ($P=0.0082$) resulted:

$$\text{Logit Risk} = -3.549227 + 0.000723 \text{ CBZ dose} + 0.000332 \text{ VPA dose} + 0.001241 \text{ LTG dose} + 0.002452 \text{ PHT dose} - 0.981189 \text{ convulsions during pregnancy}$$

Of the individual variables in the regression, only CBZ dose ($P=0.0196$) and convulsions during pregnancy ($P=0.0104$) were statistically significant, the latter associating with a decreased death hazard.

Fig 1 shows the regression line and its 95% C.I.s for risk of intrauterine death plotted against carbamazepine dose, and for comparison the 0.59% risk of intrauterine death in the unexposed pregnancies.

Discussion

The interpretation of the higher, though not statistically significantly greater, unexplained intrauterine foetal death rate in the AED-exposed as compared with the AED-untreated pregnancies in women with epilepsy is confounded by pregnancies in the latter group tending to be enrolled in the study later than pregnancies in the former group. This could have introduced into the comparison a factor of selection bias outside the control of the authors, since spontaneous abortions tend to occur mainly in the earlier weeks of pregnancy.

The present study failed to find associations between intrauterine foetal death and several potentially relevant factors, e.g. folate intake, previous spontaneous abortion, stillbirth or carrying a malformed foetus. Surprisingly, the occurrence of convulsive seizures during pregnancy was associated with a decreased foetal death hazard. Possibly low AED doses in some women had allowed convulsive seizures to occur in pregnancy, but also had reduced the risk of AED dose-related intrauterine death (shown above). The APR data do not permit assessing this possibility.

The present study investigated the possibility of an association between individual, commonly prescribed, AEDs and intrauterine foetal death. Even in the absence of plasma AED concentration data, a statistically significant ($P < .05$), and dose-related, association with carbamazepine was found, and trends in this direction for several other AEDs. This finding at first sight seems contrary to that reported in the Viale *et al*² literature meta-analysis, though in that analysis there was a higher risk of spontaneous abortion in case series where there were higher proportions of AED exposed pregnancies. The Viale *et al* analysis dealt with AEDs as a class and not with individual drugs. Considered as an overall class, in the present series AEDs also were associated with an increased, but certainly not statistically significant, relative risk of intrauterine death. That finding in the present series depended on a comparatively small number of comparison pregnancies, nearly all in women with epilepsy, whereas Viale *et al* employed substantial larger numbers of comparison pregnancies, but pregnancies of women who did not have epilepsy. Consequently the present series involves better matched, though numerically many fewer, comparators than the Viale *et al* series, and its comparator data may have been influenced by enrolment timings, as mentioned above.

The extensive data of Tomson *et al*³ lacked any AED-unexposed comparator group. Therefore no estimate of the relative risk of intrauterine foetal death associated with AED exposure was possible. That study found a statistically significantly greater risk from AED polytherapy than monotherapy, a trend found in the present study, though not to a $P < .05$ level of significance. Tomson *et al*³ found that the intrauterine death risk in monotherapy did not differ between individual commonly used AEDs, with no dose dependent risk occurring in relation to carbamazepine. In contrast, the present study found the risk associated with carbamazepine was significantly raised and dose-proportionate, and there were suggestive indications of dose-relatedness in the risks associated with valproate, lamotrigine and phenytoin (See table 1). Different AEDs and different AED doses in AED combinations in the two studies could account for discrepancies between the findings of the two studies. Interestingly, the difference regarding carbamazepine dose-relatedness was not apparent if the present monotherapy material was subdivided into the same three dosage bands that Tomson *et al*³ used, viz. <450 , $450-700$, >700 mg/day, the hazards in the present material then being 3.9%, 3.3% and 7.1% respectively. However, using <350 , $350-700$ and >700 mg/day bands, the risks became 1.7%, 4.1% and 7.1%, respectively. Choice of dosage band appears capable of influencing the outcome in this type of approach.

In view of the above, it seems that the findings of the present study are reasonably consistent with the recent literature. While they may not permit unequivocal conclusions they raise suspicion that intrauterine exposure of the foetus to some commonly used AEDs, and in particular carbamazepine, may be associated with an increased hazard of intrauterine foetal death. Whether some of these deaths depend on unrecognised foetal malformations cannot be determined from the present analysis.

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Table 1. Intrauterine foetal death rates in AED-monotherapy exposed, and unexposed, pregnancies. Data for rarely used AEDs are omitted.

Drug	N – treated	N – deaths	Deaths %	R R v No AEDs	95% C.I.
No AEDs	170	1	0.59		
Carbamazepine	404	19	4.70	8.00	1.08, 59.25
Valproate	284	9	3.17	5.39	0.65, 42.15
Lamotrigine	382	14	3.67	8.23	0.83, 47.0
Levetiracetam	129	2	1.55	2.64	0.24, 28.75
Topiramate	51	1	1.96	3.33	0.21, 52.36
Phenytoin	42	1	2.38	4.05	0.26, 63.39
Clonazepam	26	0	0	-	-
Oxcarbazepine	19	1	5.26	8.94	0.53, 137.3
Gabapentin	14	0	0	-	-

Fig 1. Logistic regression and its 95% C.I.s for risk of intrauterine death plotted against carbamazepine dose, and also the 0.59% risk of intrauterine death in the AED-unexposed pregnancies.

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Author/s:

Vajda, FJE;O'Brien, TJ;Graham, J;Hitchcock, AA;Lander, CM;Eadie, MJ

Title:

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