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Author: FJE. Vajda T.J. O'Brien J. Graham C.M. Lander MJ. Eadie

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# THE OUTCOMES OF PREGNANCY IN WOMEN WITH UNTREATED EPILEPSY

F J E Vajda [1], TJ O'Brien [1], J Graham [1], CM Lander [2], M J Eadie [2]

[1] Department of Medicine and Neurosciences, Royal Melbourne Hospital and University of Melbourne, Parkville, Victoria, 3050, [2] Royal Brisbane and Women's Hospital and School of Medicine and Biomedical Science, University of Queensland, Brisbane, Queensland, 4027, AUSTRALIA

**Corresponding Author:**

Professor FJE Vajda

**Address**: Department of Medicine and Neurosciences, Royal Melbourne Hospital and University of Melbourne, Parkville, Australia 3050

**Telephone:** 61(3).98193056

**E-mail:** vajda@netspace.net.au

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**Abstract**

Purpose: To determine the outcomes in regards to seizure control and foetal malformation in pregnant women with epilepsy not treated with antiepileptic drugs (AEDs).

Methods: Analysis of data from the Australian Register of AEDs in Pregnancy on 148 women with epilepsy who were not receiving AEDs before and during at least the first trimester of pregnancy

Results: Seizure control was less likely to be maintained in AED-untreated pregnancies. Whether AED therapy had been ceased in preparation for pregnancy, or had not been employed for long periods before pregnancy, made no statistically significant difference to seizure control outcomes, but those who ceased therapy in preparation for pregnancy were more likely to again be taking AED therapy by term.

Foetal malformation rates were reasonably similar in untreated pregnancies, and in treated pregnancies if pregnancies exposed to known AED teratogens (valproate and probably topiramate) were excluded from consideration.

Conclusions: Leaving epilepsy untreated during pregnancy appears disadvantageous from the standpoint of seizure control: it also does not reduce the hazard of foetal malformation unless it avoids valproate or topiramate intake during pregnancy.

**Key words:** antiepileptic drugs, epilepsy, foetal malformations, pregnancy, seizures

## Introduction

The extensive and continuing publicity regarding the foetal malformations associated with the use thalidomide by pregnant women in the 1960s made many women aware of the hazards of therapeutic drug intake during pregnancy. This wariness extends to antiepileptic drugs (AEDs), even though most women with epilepsy also appreciate the importance of maintaining optimal freedom from their seizures. Prior to undertaking pregnancy some women with epilepsy consider ceasing their AED therapy. Some may seek medical advice regarding the advantages and disadvantages of doing so. Others make their own unguided decisions and either reduce dosages on their own initiative or cease AEDs altogether [1]. However, there is relatively little information as to what actually happens to women with epilepsy who enter pregnancy when not taking any AED therapy.

The Australian Register of Antiepileptic Drugs in Pregnancy is concerned mainly with teratogenesis issues, but contains data on the behaviour during pregnancy of the seizure disorders of those enrolled in it. Some 8.8% of the pregnancies in women with epilepsy in the Register were not exposed to AEDs during the early months of pregnancy. Some were not exposed throughout pregnancy. We here compared what happened to the pregnancies of these untreated women with what happened to the pregnancies exposed to AED therapy throughout.

## Materials and Methods

### *The Australian Pregnancy Register*

The nature of the Australian Register of Antiepileptic Drugs in Pregnancy and its method of data collection and storage have been described previously [2-4]. The Register, which has been collecting data since 1999, is estimated to have captured some 8 to 9% of all Australian pregnancies in women with epilepsy [5]. In essence, the Register has functioned by enrolling pregnant women, the great majority of whom had epilepsy and took AEDs, and prospectively following the outcomes of their

pregnancies. These women initiated their own participation in the Register's database once they had become aware of its existence. All contact between the women and the Register was by means of telephone, with interviews on 4 occasions - at recruitment as early in pregnancy as feasible, at 7 months of gestation, in the post-partum month and, as far as possible, one year after childbirth. At each interview, in addition to material concerning the foetus, details of the patient's epilepsy, and of the occurrence and type of any epileptic seizures and the antiepileptic drugs being taken and their dosages, were recorded. Women taking AEDs for a non-epileptic indication are also enrolled on the Register, however for the present paper only women with epilepsy were studied, whether or not they were taking AEDs during the earlier months of pregnancy.

Ethical oversight of the Register has been the responsibility of the Ethics Research Committees of St. Vincent's Hospital, Melbourne, the Monash Medical Centre, and the Royal Melbourne Hospital, because the Register's site of housing has changed with time.

***Data analysis***

Data were exported from the Register's database into an Excel spreadsheet for further analysis, and statistical significances assessed by means of confidence interval analysis.

In the analyses, a distinction was made between the outcomes for seizure control during pregnancy in women with 'active' and with 'inactive' epilepsy, i.e. in women who had, and women who had not experienced seizures during the previous 12 months. It had been observed previously that the prognosis for seizure freedom during pregnancy was quite different, depending on whether or not a woman had suffered seizures during her pre-pregnancy year [6-8]. In the present series, seizures had occurred during pregnancy in 79.2% of pregnancies associated with less than 1 year of pre-pregnancy seizure freedom, but in progressively lower proportions of those with longer periods of seizure freedom (in 23% of those with at least 1 year's freedom, in 20.5% with 2 years' freedom, in 19% with

3 years' freedom, in 17.5% with 4 years' freedom and in 17.7% with 5 or more years seizure-freedom).

**Results**

Of 1720 pregnancies in women with epilepsy included in the Australian Register, 148 (8.8%) were not exposed to AEDs at the time of conception. Various characteristics of the pre-pregnancy circumstances and the pregnancies, and the associated seizure disorders in the AED untreated and AED treated groups, are compared in Table 1 In general, the two groups seemed reasonably similar in composition in relation to the parameters considered. However, the AED treatment in the untreated group had been changed more often before pregnancy than in the treated group (because by definition being in the untreated group itself often involved a treatment change, viz. withdrawal of therapy). Members of the untreated group were more likely to have experienced epileptic seizures of any type during pregnancy (56.1% *versus* 46.9%). There were no statistically significant differences between the types of seizure disorder involved, the occurrence rates of convulsive seizures at some stage during pregnancy, and of the behaviours of active and inactive epilepsies. Those not taking antiepileptic drugs were also less likely to have taken folate before pregnancy. Foetal malformations were half as frequent in the untreated group as in the AED treated pregnancies, but the difference was not statistically significant. When pregnancies associated with continuing intake of valproate and topiramate, both known teratogens [9], were excluded, there was little difference in the rate of foetal malformations between the AED treated and untreated pregnancies. On the other hand, in comparison with pregnancies exposed to valproate and/or topiramate, the risk of foetal malformation was statistically significantly lower in the untreated pregnancies.

Within the 148 pregnancies not treated with AEDs at the time of conception a number of features, mainly concerning seizure activity, were compared between the women whose seizure disorders were active before pregnancy and those whose disorders were inactive (Table 2). The only significant difference between the two groups was a considerably higher rate of seizure occurrence during

pregnancy in the women with already active epilepsies at entry into pregnancy (any seizures: 82.4% *versus* 29.7%; convulsive seizures: 36.5% *versus* 12.2%). The epilepsy history for women who had active epilepsy before their untreated pregnancies were of shorter mean duration (10.6 *versus* 14.1 years), and by term were more often being treated with AEDs (55.4% *versus* 37.8%).

There were 62 of the 148 pregnancies (41.9%) in women who had elected to cease AED treatment shortly prior to pregnancy. Nearly all of these women indicated that they wished to avoid drug intake during pregnancy. The remaining untreated pregnancies were in women with epilepsy that was either previously untreated or in whom treatment had been ceased well before pregnancy. Half of the women who were untreated in the longer term had undergone previous pregnancies. Only four of these 43 (9.3%) had taken AEDs in previous pregnancies. This suggested that there was a group of women who followed a consistent pattern of reluctance to take AEDs. The outcomes of the two subsets of untreated pregnancies are compared in Table 3

Those who deliberately ceased AED treatment in preparation for pregnancy had a slightly younger mean age than those who had been untreated over longer periods. There were no significant differences between the rates of occurrence of the major types of seizure disorder in two groups, or in the proportions of each group who had seizures during pregnancy. More who had ceased treatment as a pre-pregnancy precaution were found to have resumed AED therapy by the end of pregnancy (56.4% *versus* 39.5%). The data suggested that having seizures during pregnancy in those who had ceased AEDs before pregnancy increased the likelihood that AED therapy would be resumed by the end of pregnancy (83.3% v 31.3%; R.R. = 2.67, 95% C.I. = 1.56, 4.57). The same applied for those with longer term non-use of AEDs (54.7% v 15.2%; R.R. = 3.61, 95% C.I. = 1.55, 8.40).

Foetal malformation rates were too low to permit conclusions regarding differences in teratogenesis hazard between the two patterns of untreated pregnancies, or between treated and untreated pregnancies if the effects of valproate and topiramate exposure, as mentioned above, were excluded

**Discussion**

Since the review of Schmidt [10] more than 30 years ago, a number of papers have been published concerning the effects of pregnancy on epileptic seizure control (e.g. [7]), but almost all of these applies to AED-treated epilepsy. There is a paucity of quantitative data on untreated epilepsy in pregnancy that can be compared with the findings of the present study. So long as it is accepted that AEDs can prevent epileptic seizures, some outcomes of the study described are as expected, e.g. that those who were not taking AEDs at the outset of pregnancy would be more likely to have seizures during pregnancy than those who had similar degrees of seizure activity before pregnancy but continued to take AEDs. It might also have been anticipated that there would have been more difference than was found in the rates of seizure occurrence in pregnancy between those who had recently ceased antiepileptic drug treatment in anticipation of pregnancy and those who had not taken antiepileptic drugs for a longer time, if ever.

The number of untreated pregnancies in the present study is comparatively small, relative to the number of treated pregnancies, though this represents the outcome of 15 years of nationwide voluntary data collection. To delay analysis till sufficient numbers had been accumulated to significantly increase the statistical power of the study would probably involve a prohibitively long period during which therapeutic practice might change. Because of comparatively small numbers in the untreated group, failure to detect statistically significant differences in some parameters studied may not necessarily mean that real differences do not exist, particularly when relative risk values are near a 95% confidence interval limit. Thus there was a statistically significant increase risk of any type of seizure occurring during pregnancy in the untreated group (relative risk 1.20; 95% confidence interval 1,03, 1.39). However in the component subsets of this group, one where seizures had occurred in the year before pregnancy and the other where they had not occurred, the differences did not achieve statistical significance. It is also possible that in some of the pregnancies that fell into the treated category, the women involved may not have been fully compliant with prescribed therapy. If

so, this may have decreased the true differences in seizure occurrence rates between the untreated and treated groups, when the rates in the untreated group already tended to be higher.

The chance of having seizure during childbirth was very similar for women who had been seizure free compared with those who had not been seizure free in the year prior to pregnancy. The chances was also little different in women who had ceased antiepileptic drug intake for pregnancy and those who had not been taking the drugs well before the onset of pregnancy. However, the interpretation of these findings is confounded by the fact that more women with active epilepsies before pregnancy, and those who ceased the drugs intending to become pregnant, had resumed the drugs before childbirth.

It appeared that the main determinant of the outcome regarding seizure occurrence in AED-untreated pregnancy was not so much the length of time before pregnancy over which no AED treatment was taken, but whether the women's epilepsy was active or inactive when they entered pregnancy. If the epilepsy was active, women would probably tend to experience further seizures during pregnancy so that the disadvantages and hazards that they were already experiencing would continue. If the epilepsy prior to pregnancy was inactive, the women seemed to have less risk of having seizures during pregnancy than the women whose pre-pregnancy epilepsy was active. However, the women with inactive epilepsy still had about a 30% risk of seizures in pregnancy. This risk appeared greater, though not statistically significantly so, than the risk of seizures returning in pregnancy in the women with inactive pre-pregnancy epilepsy who continued to take antiepileptic medication in pregnancy. The untreated women with inactive epilepsy would probably have proportionately more to lose from having their seizures recur during pregnancy than the women with already active epilepsy, since the former would then face additional disadvantages, including the possibilities of physical injury during seizures, and possible sudden unexpected death, and would also have restrictions imposed on their lifestyle activities, including vehicle driving.

In conclusion the experience of the present series suggested that while ceasing AEDs that are known teratogens, such valproate and possibly topiramate, in anticipation of pregnancy may decrease the risk

of having a foetal malformation, for the less teratogenic medication the risk to the foetus of continuing the medication may be positively outweighed by the improvement in seizures control for the mother. This is particularly true for women whose epilepsy was active in the year prior to the pregnancy. This information may help inform women with epilepsy weighing up the risks and benefits of withdrawal of AED therapy in preparation for pregnancy.

**Disclosure of Conflicts of Interest:**

None of the authors has any conflict of interest to disclose

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**Disclosure of Conflicts of Interest:**

None of the authors has any conflict of interest to disclose

Table 1: Characteristics of the untreated and AED treated pregnant women with epilepsy, their epilepsies and foetal outcomes as far as malformation was concerned. The likelihood of various items occurring is expressed relative to that for the treated women.

| | No AEDS | P<.05 | AEDs | R.R. or Difference | 95% C.I. |
|---|---|---|---|---|---|
| Number | 148 | | 1532 | | |
| Mean Age (years) | 30.74 | | 30.69 | -0.05[#] | -1.02, +1.12 |
| Referral source– neurologist | 51.4% | | 47.9% | 1.07 | 0.91, 1.26 |
| Referral source– other medical practitioner | 12.2% | | 15.9% | 0.77 | 0.49, 1.20 |
| Pregnancy number – 1 | 46.6% | | 41.6% | 1.12 | 0.93, 1.34 |
| Pregnancy number – 2 | 32.4% | | 29.6% | 1.09 | 0.86, 1.40 |
| Pregnancy number – 3 | 11.5% | | 16.1% | 0.71 | 0.45, 1.49 |
| Pregnancy number – 4 | 6.1% | | 7.1% | 0.85 | 0.44, 1.65 |
| Pregnancy number - >4 | 3.4% | | 5.4% | 0.62 | 0.25, 1.49 |
| Pregnancies 1 and 2 combined | 79.1% | > | 73.1% | 1.11 | 1.01,1.21 |
| Assisted fertilisation involved | 5.4% | | 5.8% | 0.93 | 0.43, 1.68 |
| Previous malformed offspring (N=79, 894) | 2.5% | | 4.8% | 0.53 | 0.13, 2.13 |
| Previous neonatal deaths (N=79, 894) | 1.3% | | 0.8% | 1.62 | 0.20, 12.97 |
| Epilepsy duration ( mean in years) | 12.3 | < | 14.1 | -1.80[#] | -3.25, -0.35 |
| Epilepsy type – partial | 44.6% | | 49.0% | 0.91 | 0.76, 1.10 |
| Epilepsy type – generalised | 45.9% | | 42.5% | 1.08 | 0.90, 1.30 |
| Epilepsy type – uncertain | 9.5% | | 8.6% | 1.11 | 0.65, 1.07 |
| AED change before pregnancy | 41.9% | > | 14.2% | 3.03 | 2.42, 3.79 |
| Preconception folate intake | 65.5% | < | 70.8% | 0.85 | 0.75, 0.98 |
| Seizures during pregnancy – any | 56.1% | > | 46.9% | 1.20 | 1.03, 1.39 |
| Seizures during pregnancy – convulsive | 24.3% | | 18.9% | 1.29 | 0.95, 1.74) |
| *Active epilepsy before pregnancy* | 50.0% | | 43.6% | 1.15 | 0.97, 1.36 |
| Seizures during pregnancy – any | 82.4% | | 79.1% | 1.04 | 0.93, 1.16 |
| Seizures during pregnancy – convulsive | 36.5% | | 32.8% | 1.13 | 0.81, 1.53 |
| Seizures during birth | 2.7% | | 3.6% | 0.75 | 0.18, 3.12 |
| *Inactive epilepsy before pregnancy* | 50.0% | | 56.4% | 0.89 | 0.75, 1.05 |
| Seizures during pregnancy – any | 29.7% | | 21.9% | 1.36 | 0.94,1.97 |
| Seizures during pregnancy – convulsive | 12.2% | | 8.2% | 1.48 | 0.77, 2.84 |
| Seizures during birth | 3.4% | | 0.9% | 2.92 | 0.63, 13.50 |
| *Malformed foetus* | 3.4% | | 7.1% | 0.47 | 0.20, 1.15 |
| Malformed foetus [@] | 3.4% | | 4.5% | 0.74 | 0.30, 1.84 |
| Malformed foetus [$] | 3.4% | < | 12.1% | 0.28 | 0.11, 0.68 |

# A difference, not a R.R. value [@] Pregnancies exposed to VPA and TPM excluded $ pregnancies exposed to VPA or TPM

Table 2: Comparisons between women with active and inactive epilepsies that were not treated with AEDs, at least in earlier pregnancy. The likelihood (R.R.) of various items occurring in the active epilepsy group is expressed relative to that for the women with inactive epilepsies.

| | Active Epilepsy | P<.05 | Inactive Epilepsy | R.R or Difference | 95% C.I. |
|---|---|---|---|---|---|
| Number | 74 | | 74 | | |
| Mean Age (years) | 30.1 | | 31.4 | -1.30 # | -2.85, 0.25 |
| Referral source– neurologist | 54.1% | | 48.6% | 1.11 | 0.81, 1.52 |
| Referral source– other medical | 16.2% | | 8.1% | 2.00 | 0.79, 5.05 |
| Pregnancy numbers – 1 or 2 | 78.4% | | 79.7% | 0.98 | 0.83, 1.16 |
| Pre-conception folate intake | 59.5% | | 74.3% | 0.80 | 0.64, 1.01 |
| Epilepsy – partial | 47.3% | | 41.9% | 1.13 | 0.79, 1.62 |
| Epilepsy-generalised | 41.9% | | 50.0% | 0.84 | 0.59, 1.19 |
| Epilepsy-type uncertain | 10.8% | | 8.3% | 1.30 | 0.47, 3.55 |
| Epilepsy duration (mean in years) | 10.6 | < | 14.1 | -3.50 # | -6.54, +0.46 |
| Seizures during pregnancy – any | 82.4% | > | 29.7% | 4.00 | 2.39, 6.70 |
| Seizures during pregnancy – convulsive | 36.5% | > | 12.2% | 3.00 | 1.52, 5.93 |
| Seizures during birth | 2.7% | | 2.7% | 1.00 | 0.14, 6.91 |
| Taking AEDs by 7 months | 53.1% | > | 29.7% | 1.79 | 1.18, 2.72 |
| Taking AEDs by term | 55.4% | > | 37.8% | 1.46 | 1.03, 2.09 |
| Taking AEDs by term – had seizures | 51.2% | | 57.1.4% | 0.90 | 0.58, 1.39 |
| Foetal Malformations | 2.7% | | 4.1% | 0.67 | 0.11, 3.87 |

# = a difference, not a RR

Table 3.Comparison of various differences between women who ceased AEDs in preparation for pregnancy, and those who were not taking AEDs well before the commencement of pregnancy

| | Came off AEDS | P<.05 | Not on AEDS | R.R. or Difference | 95% C.I. |
|---|---|---|---|---|---|
| Number | 62 | | 86 | | |
| Mean Age (years) | 29.7 | < | 31.5 | -1.80 # | -3.36, -0.24 |
| Referral source– neurologist | 51.6% | | 51.2% | 1.01 | 0.73, 1.39 |
| Referral source– other medical | 9.7% | | 14.0% | 0.69 | 0.28, 1.75 |
| Pregnancy numbers – 1 or 2 | 82.3% | | 76.7% | 1.07 | 0.91, 1.26 |
| Pre-conception folate intake | 72.6% | | 60.5% | 1.20 | 0.95, 1.51 |
| Pre-pregnancy active epilepsy | 45.2% | | 47.7% | 0.95 | 0.67, 1.35 |
| Epilepsy – partial | 45.2% | | 44.2% | 1.02 | 0.71, 1.47 |
| Epilepsy-generalised | 43.55% | | 47.6% | 0.91 | 0.64, 1.31 |
| Epilepsy-type uncertain | 11.35% | | 3.5% | 3.24 | 0.87, 12.03 |
| Epilepsy duration (mean, in years) | 12.9 | | 11.9 | +0.9 # | -2.23, +4.03 |
| Seizures during pregnancy – any | 48.4% | | 61.6% | 0.79 | 0.58, 1.07 |
| Seizures during pregnancy – convulsive | 21.0% | | 26.7% | 0.78 | 0.43, 1.42 |
| Seizures during birth | 3.2% | | 2.3% | 1.39 | 0.20, 9.58 |
| Taking AEDs by 7 months | 43.5% | | 35.7% | 1.29 | 0.86, 1.95 |
| Taking AEDs by term | 56.4% | > | 39.5% | 1.43 | 1.02, 2.01 |
| Taking AEDs by term – had pregnancy seizures | 83.3% | > | 54.7% | 1.52 | 1.14, 2.04 |
| Taking AEDs by term – no pregnancy seizures | 31.3% | | 15.2% | 2.06 | 0.79, 5.37 |
| Foetal Malformations | 1.6% | | 4.7% | 0.35 | 0.04, 3.03 |

# = a difference, not a RR

**Highlights**

- Some women with epilepsy cease AED therapy shortly before and during pregnancy
- Some others have taken no AEDs since well before pregnancy
- Seizure control was worse if seizures occurred in pre-pregnancy year
- Excepting VPA and TPX, avoiding AEDs does not reduce malformation risk