

Predicting epileptic seizure control during pregnancy

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ABSTRACT

Objective: The objective of the study was to assess whether the type of seizure disorder present in the prospective mother with epilepsy, her use of antiepileptic drugs (AEDs) in early pregnancy, and her seizure control before pregnancy help predict her prospects for seizure freedom throughout pregnancy.

Methods: This paper is based on data accumulated in the Australian Pregnancy Register (APR) between 1998 and late 2016. Information was analyzed concerning epileptic seizure occurrence and AED therapy taken before and during pregnancy, using simple statistical and confidence interval (C.I.) methods, mainly relative risk (R.R.) calculations.

Results: After excluding pregnancies lost to follow-up, and those that ended prematurely because of spontaneous abortion or stillbirth, 1939 pregnancies were available for study. Seizures had occurred during pregnancy in 829 (42.8%), and convulsive seizures in 385 (19.9%). Seizures of any type occurred in 78.4% of pregnancies where seizures had occurred in the previous year (active epilepsy) and in 22.3% of those associated with inactive epilepsy. Seizures of any type had occurred in 54.9% of pregnancies initially unexposed to AEDs and in 45.5% of those treated with AEDs throughout. The corresponding figures for convulsive seizures during pregnancy were 31.7% and 22.3%. There was statistically significant evidence that, in women with epilepsy (WWE), having a seizure disorder that was active in the prepregnancy year and one untreated in early pregnancy was associated with decreased prospects of seizure freedom during pregnancy. Decreased chances of seizure-free pregnancies in women with focal epilepsies and those treated with multiple AEDs were probably explained by greater frequencies of active seizure disorders in these patient categories.

Conclusions: Women with epilepsy who experience seizures in the year prior to pregnancy appear 3 or 4 times more likely to continue to have seizures during pregnancy than women whose seizures are fully controlled prior to pregnancy. Not taking AEDs in early pregnancy also increases the hazard for seizure occurrence in pregnancy.

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1. Introduction

Recent studies show that most of the pregnancies of women with epilepsy (WWE) remain seizure-free under contemporary methods of management, and information derived from the Australian Pregnancy Register (APR) [1,2] and from other sources [3,4] indicates that seizure control *prior to pregnancy* is a significant factor in determining such seizure control during pregnancy.

Our previous analysis in 2008 [1] was based on the 841 pregnancies then available in the APR. The APR now contains information on more than double that number of pregnancies. An analysis of its current enlarged database was, therefore, carried out, hoping to ascertain whether it might be possible to refine the prediction of seizure control

throughout pregnancy. We employed information available prior to pregnancy in addition to previous seizure control and its duration, for instance the type of seizure disorder present in the prospective mother and her use or nonuse of antiepileptic drugs (AEDs).

2. Materials and methods

This paper is based on data accumulated in the APR between 1998 and late 2016. Detailed information regarding the Register is available elsewhere. Enrolment in it is at the discretion of women after they have been referred from professional and lay sources. The Register has been estimated to have collected information on about 8.7% of the relevant pregnancies that occurred in Australia during its existence [5]. All participant contact with the Register is by telephone. The information about the course of pregnancy that has been utilized in this paper was recorded at the initial contact with the Register, again at approximately 28 weeks of pregnancy, then within the first postpartum month. The accuracy of information provided by pregnant women has been checked with their treating doctors. Register personnel have not attempted to

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influence the clinical management of the pregnancies. The Register has been under the ethics oversight of various Melbourne-based institutional ethics committees and currently is under the aegis of Melbourne Health.

The primary purpose of the Register is to investigate the relationship between AED exposure in pregnancy and fetal malformation, but information is also collected concerning details of the epilepsies present, epileptic seizure occurrence, and AED therapy taken before and during pregnancy. The presence or absence of any type of epileptic seizure and of convulsive seizures (which may be more reliably remembered) is recorded. The numbers of seizures in individual pregnancies are not available for analysis since it was not considered practicable to ask WWE to keep seizure diaries both before and throughout pregnancy to obtain seizure counts. The available information was analyzed employing simple statistical and confidence interval (C.I.) methods, mainly relative risk (R.R.) calculations.

3. Results

3.1. Pregnancies studied

After excluding pregnancies lost to follow-up, and those that ended prematurely because of spontaneous abortion or stillbirth, there were 1939 pregnancies available for study. Seizures had occurred during pregnancy in 829 (42.8%) of these, including convulsive seizures in 385 (19.9%). There also were intrapartum seizures in 40 (2.1%) of the pregnancies, 5 occurring in ones that had been seizure-free not only throughout pregnancy but also for at least a year prior to that. No AEDs were taken throughout 2 of these 5 pregnancies. This subgroup of 5 pregnancies was too small for further analysis.

3.2. Type of epilepsy

The epilepsy type was generalized in 43.3% of the pregnancies, focal (partial) in 48.4%, and uncertain in 8.3%. Seizures occurred during pregnancy in 40.1% of the generalized epilepsy pregnancies, and in 52.5% of the focal epilepsy ones, a higher R.R. of seizures in pregnancy for the latter (1.31; 95% C.I. of 1.18, 1.45). The corresponding figures for convulsive seizures were 23.4% for generalized epilepsies and 22.2% for focal epilepsies (R.R. = 0.94; 95% C.I. 0.79, 1.12).

3.3. Seizure disorder activity before pregnancy

The rates of occurrence of any seizures, and of convulsive seizures, were plotted against the reported duration of freedom from seizures prior to pregnancy (Fig. 1). The decreases in the hazards of seizure-affected pregnancy with increasing durations of pre-pregnancy seizure freedom appear to be adequately described by monoexponential decay

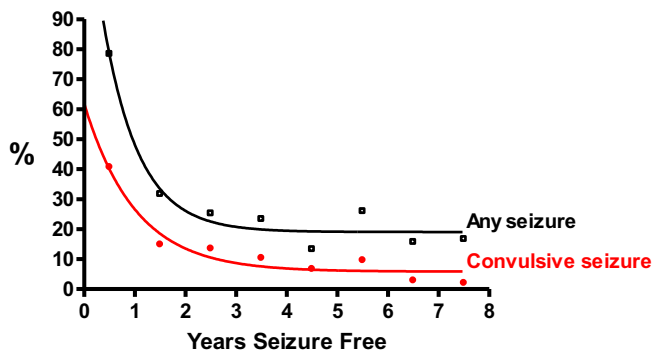


Fig. 1. Relationships between percentages of pregnancies in which (i) seizures of any type and (ii) convulsive seizures occurred during pregnancy, and duration of seizure freedom prior to pregnancy.

processes. Most of the risk of seizures in pregnancy was associated with pre-pregnancy seizure-free periods of less than 1 year. Being more than 2 years without seizures before pregnancy seemed to offer negligible further advantage from the standpoint of achieving seizure-free pregnancy. For the purposes of the present paper, seizure disorders where seizures occurred in the pre-pregnancy year were regarded as 'active' epilepsies, and those with longer periods without seizures before pregnancy as 'inactive' epilepsies.

Seizures of any type had occurred in 78.4% of pregnancies associated with active epilepsy, and in 22.3% of those associated with inactive epilepsy (R.R. = 3.51; 95% C.I. 3.13, 3.94). The corresponding figures for convulsive seizures during pregnancy were 40.7% and 10.1% (R.R. = 4.02; 95% C.I. 3.31, 4.88).

The seizure disorder present was active in 37.1% of the 839 pregnancies in women with generalized epilepsy, and in 48.0% of the 939 pregnancies in women with focal epilepsies (odds ratio = 0.64; 95% C.I. = 0.53, 0.71).

3.4. AED use

At the commencement of pregnancy, 164 (8.5%) of the women involved were not taking AEDs. Of this subgroup, 43.9% resumed therapy during the course of pregnancy, the resumption usually being associated with the occurrence of seizures. Because the interest of the present paper lies in the situation at the outset of pregnancy, this matter of resumption of therapy is not considered further.

Seizures had occurred in 54.9% of the pregnancies initially unexposed to AEDs, and in 45.5% of those exposed to AEDs throughout pregnancy (R.R. = 1.21; 95% C.I. 1.04, 1.40). The corresponding figures for convulsive seizures during pregnancy were 31.7% and 22.3% (R.R. = 1.41; 95% C.I. 1.11, 1.80).

The pre-pregnancy seizure disorder was active in 43.9% of the pregnancies that were at least initially untreated, and in 42.2% of the ones treated throughout pregnancy.

3.5. Effects of seizure risk factors in combination

In the WWE, having focal epilepsy, having a seizure disorder that was active in the pre-pregnancy year, and not being treated with AEDs, were individually associated with increased hazards of seizures occurring during pregnancy. However, these individual factors existed together in the pregnancies. Figs. 2 (for any seizures) and 3 (for convulsive seizures) show the likelihoods of seizures of any type and convulsive seizures occurring during pregnancy when the criteria of (i) type of epilepsy, (ii) activity of seizure disorder in the pre-pregnancy year, and (iii) AED treatment in at least the earlier half of pregnancy are applied sequentially to the APR data.

From the inspection of Figs. 2 and 3, it seems that activity of epilepsy prior to pregnancy was the major determinant of the hazard of seizure-affected pregnancy, that being untreated with AEDs at the outset of pregnancy made a small additional contribution to the hazard, while any increased seizure hazard from having focal epilepsy hardly existed after pre-pregnancy seizure disorder activity had its effects.

3.6. AED polytherapy

The effect of taking AEDs either in monotherapy (72.1% of all treated pregnancies) or in drug combinations (27.9%) was explored. Explicit information was not available to explain why AED polytherapy had been employed in particular women, but 59.1% of the polytherapy pregnancies, and only 36.3% of the monotherapy ones, had active epilepsy before pregnancy (R.R. = 1.62; 95% C.I. 1.47, 1.81). Therefore, polytherapy may have sometimes been employed because of failure of AED monotherapy. Pregnancies in which any type of seizure, and convulsive seizures, had occurred were more frequent in the polytherapy group than the monotherapy one (any type of seizure – 62.6% versus 37.5%; R.R. = 1.67; 95%

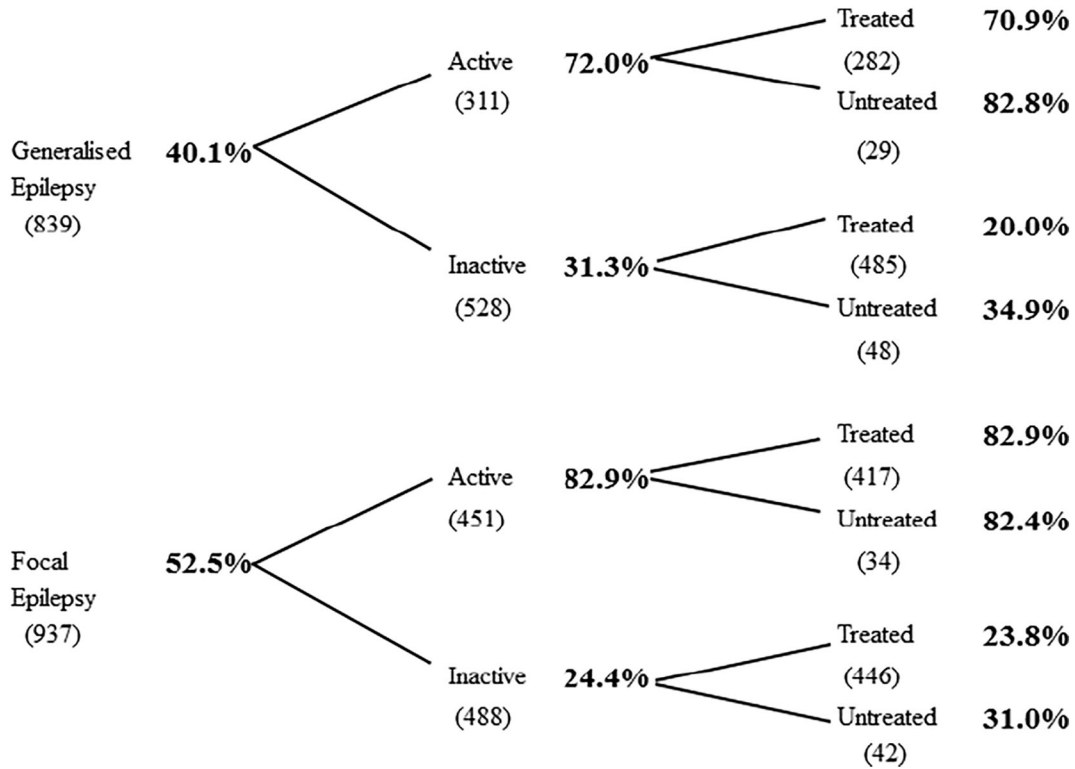


Fig. 2. Chance of seizures of any type occurring during pregnancy. Numbers in parentheses refer to numbers of pregnancies from which each following percentage value is derived.

C.I. 1.51, 1.85, and convulsive seizures 35.2% versus 23.7%: R.R. = 1.48; 95% C.I. 1.27, 1.73). Where there was prepregnancy active epilepsy, the rates of occurrence of seizure-affected pregnancy were a little higher in the polytherapy group than in the monotherapy one (84.9% versus 73.5%: R.R. = 1.16; 95% C.I. 1.07, 1.24). A higher risk also applied

for polytherapy in inactive epilepsy-associated pregnancies, but with substantially lower seizure-affected pregnancy rates (30.2% versus 19.2%: R.R. = 1.57; 95% C.I. 1.22, 2.02).

Too many individual AEDs and AED combinations were involved during pregnancy, sometimes in changing dosages, for it to be

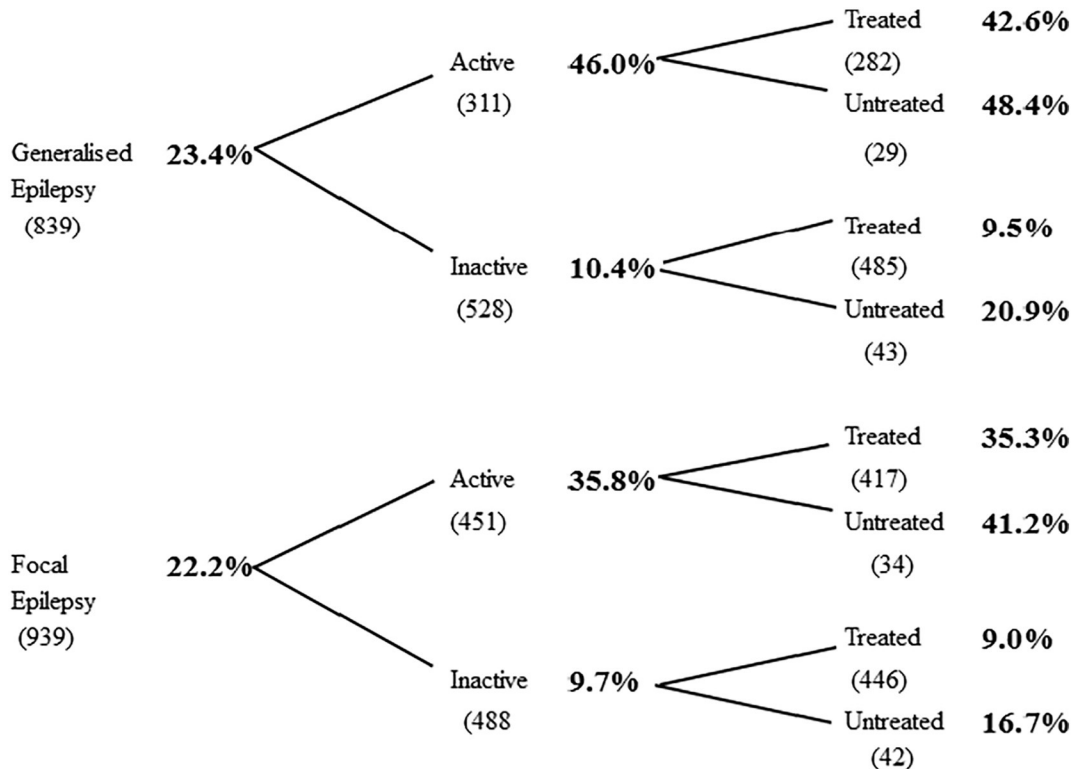


Fig. 3. Chance of convulsive seizures occurring during pregnancy. Numbers in parentheses refer to numbers of pregnancies from which each following percentage value is derived.

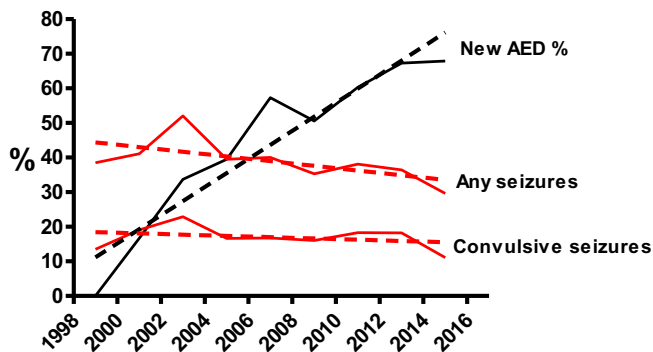


Fig. 4. Changes with time in the percentages of pregnancies (i) exposed to one or more newer (i.e., postvalproate) AEDs, (ii) experiencing seizures of any kind, and (iii) experiencing convulsive seizures during pregnancy, with the associated linear regression lines.

practicable to use the APR data to assess the contributions of particular AED in the combinations to seizure control.

3.7. Effect of newer AEDs

In pregnancies exposed to AED monotherapy, it was possible to investigate whether the advent of newer (i.e., postvalproate) AEDs (mainly lamotrigine, topiramate, levetiracetam, gabapentin, oxcarbazepine) was associated with altered seizure control rates during pregnancy.

Linear regressions were fitted to the rates of employment of the newer AEDs in monotherapy and the rates of pregnancies in which any type of seizure, and convulsive seizures occurred over the years during which the APR had collected data (Fig. 4). The considerable progressive increase in employment of newer drugs was not associated with any statistically significant decline in the rate of occurrence of seizure-affected pregnancies.

4. Discussion

4.1. Study limitations

The data on which the present paper is based were drawn from a pregnancy register that collected information from voluntarily enrolled women. The pregnancies studied may, therefore, not necessarily be representative of pregnancy in Australian WWE. The majority of the pregnancies were referred to the Register by neurologists or information was available that the seizure disorders present had been managed by neurologists. Therefore, the epilepsies involved probably had been managed, at least around the time of recruitment into the register, in accord with what could be regarded as optimal contemporary practice.

While the accuracy of some of the information obtained could be checked with the women's treating doctors, some of it inevitably depended on the correctness of women's memories regarding seizure occurrence. It was not practicable to persuade large numbers of pregnant women to keep seizure diaries, and in any event, this could not have been done for seizures, which had occurred prior to recruitment into the APR [6]. Therefore, the occurrence or nonoccurrence of any type of seizure and of convulsive seizures was the most reliable measure of seizure activity that could be studied. It is also probably the most significant issue from the pregnant woman's point of view, in that full freedom from all seizures over a substantial period of time opens a prospect that the underlying seizure disorder has gone into remission. It also makes possible, under contemporary Australian conditions, for the woman to hold a driving license. This is a particularly important matter in a country where there is a considerable scatter of population over long distances and where public transport, even in urban areas, is not particularly well-developed [7].

The criterion of seizure disorder activity that was employed is arbitrary, but practical both in terms of the information contained in Fig. 1, and in obtaining information from women regarding their seizures in the 12 months before pregnancy.

4.2. Findings

The major findings of the present study, in relation to predicting epileptic seizure control in pregnant women, relate to the activity of the underlying seizure disorder, the type of epilepsy suffered, whether the epilepsy is treated in the earlier part of pregnancy, and whether the treatment involves AED polytherapy. As previously known [1,2,3,4], it appears that the activity of the epileptic process in a given woman prior to pregnancy is a significant and, in the present investigation, the main factor in determining whether a woman with epilepsy will have seizures during pregnancy. While women with focal epilepsies appeared more likely to have seizure-affected pregnancies, they were also more likely to have active epilepsies before becoming pregnant. Consequently, the type of epilepsy in its own right may not be a significant factor in determining whether seizures occur during pregnancy. Not taking AED in early pregnancy appears to produce a slightly increased further hazard from the seizure control viewpoint. The interpretation of this finding is not confounded by the presence of different proportions of women with active and inactive underlying seizure disorders in the treated and untreated groups. However, the increased likelihood of seizures during pregnancy in women taking AED polytherapy when pregnancy commenced is probably explained by such women having more active epilepsies in the first place.

4.3. Conclusions

If the information from the present study is applied to WWE who are planning pregnancy, or who are in early pregnancy, it might be anticipated that those who had experienced seizures in the year prior to pregnancy would be 3 or 4 times more likely to continue to have seizures during pregnancy than women with already fully controlled seizure disorders prior to pregnancy. Not taking AEDs in early pregnancy would increase the hazard for seizure occurrence to a relatively small extent, but it might also reduce the known hazards of impaired fetal structural integrity and possibly intellect. The type of maternal epilepsy present and the use of AED combinations appear comparatively unimportant in relation to predicting seizure freedom during pregnancy.

This information may help in advising WWE who are considering or undertaking pregnancy. It emphasizes the desirability of obtaining continuing full seizure control prior to pregnancy.

Disclosure of conflict of interest

F.J.E. Vajda has received research support for the APR from the Epilepsy Society of Australia, RMH Neuroscience Foundation, Epilepsy Action, Sanofi-Aventis, UCB Pharma, Eisai, and Sci-Gen.

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C.M. Lander, J.E. Graham, A.A. Hitchcock, and M.J. Eadie have no relevant conflicts of interest to declare.

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