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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.

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 prepregnancy seizure freedom appear to be adequately described by monoexponential decay processes. Most of the risk of seizures in pregnancy was associated with prepregnancy 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 prepregnancy year were regarded as 'active' epilepsies, and those with longer periods without seizures before pregnancy as 'inactive' epilepsies.

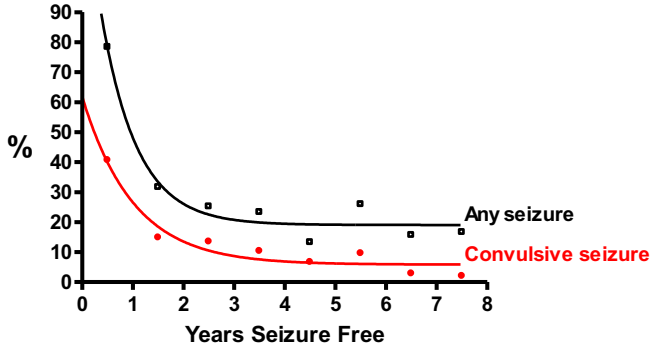

Fig. 1. Relationships between percentages of pregnancies in which (i) seizures of any type and (ii) convulsive seizures occurred during pregnancy, and duration of seizure freedom prior to pregnancy.

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 prepregnancy 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 prepregnancy 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 prepregnancy 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 prepregnancy 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%