Epilepsia, 49(1):172–175, 2008
doi: 10.1111/j.1528-1167.2007.01412.x

BRIEF COMMUNICATION

Seizure control in antiepileptic drug-treated pregnancy

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SUMMARY

This brief report covers an analysis of 7 years outcome data from the Australian Register of Antiepileptic Drugs in Pregnancy. In studying the control of antiepileptic drug-treated epileptic seizures during pregnancy, it was found that pregnancy had little influence on antiepileptic drug-treated epileptic seizure disorders. Seizures during pregnancy occurred in 49.7% of 841 antiepileptic drug (AED) treated pregnancies in women with epilepsy. Epilepsies that were active in the year before pregnancy tended to increase the risk of intrapartum and postpartum seizures. The risk of seizures during pregnancy was 50–70% less if the prepregnancy year was seizure free, and decreased relatively little more with longer periods of prepregnancy seizure control. Once there had been 1 year's freedom from seizures there seemed relatively little further advantage in deferring pregnancy to avoid seizures returning while pregnant.

KEY WORDS: Epilepsy, Register, Women, Outcomes, Seizure freedom.

The literature indicates some controversy about the worsening or improvement of epilepsy during pregnancy (Knight & Rhind 1975; Schmidt, 1982; Gjerde et al., 1988; Scheffler 1990; Vidovic & Della Marina, 1994; Costa et al., 2005). We present here outcome data from the Australian Register of Antiepileptic Drug Treated Pregnancies to assess the behavior of epileptic seizures from a substantial series of 841 antiepileptic drug (AED)-treated pregnancies in women with epilepsy (WWE). This may help guide practitioners managing epilepsy in pregnancy.

MATERIALS AND METHODS

Since 1999, the Australian Register (Vajda et al., 2006) has collected data on fetal malformations in the offspring of AED-treated pregnancies in WWE, in women who did not have epilepsy, and in WWE untreated during pregnancy. The Register has been under the ethics oversight of the research ethics committees of St. Vincent's Hospital and subsequently of Monash University, Melbourne. Recruitment into the Register has been entirely voluntary, pregnant women being referred by medical practitioners, lay organizations, or learning about the project via advertisements or from nurses or fellow patients. All patient contact with the Register has been by telephone, with interviews at recruitment, at 28 weeks of pregnancy, at 4 weeks postpartum, and at 1 year after childbirth. Data on personal, occupational, past, family, medical, obstetric, social, nutritional, and recreational activities were obtained, especially as relevant to epilepsy, Data were recorded in a computerized proforma, into which at interview details of the seizure disorder present, whether seizures had occurred, and other relevant information, were included. Keeping detailed seizure diaries, although attempted, proved impracticable. Medical details were confirmed by contact with treating medical practitioners. Patients' identifying data were kept in a separate register, for confidentiality.

Relevant details of the patients' epilepsies and other characteristics were extracted from the Register database into Excel spreadsheets. Data analysis utilized linear regression or confidence interval methods.

Accepted September 18, 2007; Online Early publication November 21, 2007.

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Table 1. Various characteristics of the 418 pregnancies that had seizures during, compared with the same characteristics in the 423 pregnancies that were seizure-free. Values in the upper four rows are years ± SDs, and in the remaining rows percentages

Characteristic	Seizures-during	Seizure-free	Difference or relative risk	95% C.I.	p value
Mean maternal age (years)	30.08 ± 4.61	30.87 ± 4.47	0.79	0.18, 1.40	<0.05
Mean epilepsy onset age (years)	15.04 ± 8.66	17.05 ± 7.89	2.01	0.89, 3.13	<0.01
Mean epilepsy duration (years)	15.09 ± 8.91	13.83 ± 8.05	−1.26	−2.40, −0.12	<0.05
Mean prepregnancy seizure free (years)	1.04 ± 2.65	3.63 ± 3.91	2.57	2.02, 3.02	<0.01
Taking more than 1 AED	35.41	15.84	2.24	1.72, 2.88	<0.01
Referred by neurologist	54.78	45.86	1.19	1.04, 1.37	<0.05
Generalized epilepsies (%)	40.43	50.83	0.80	0.69, 0.92	<0.01
Partial epilepsies (%)	55.02	42.08	1.31	1.14, 1.51	<0.01

Results

At the time of analysis the Register contained details of 1,002 pregnancies, 841 in WWE who took AEDs throughout pregnancy. The present paper is based on these 841 pregnancies only. There were no instances of gestational epilepsy.

At least one seizure occurred during 418 of the 841 pregnancies studied (49.7%). In 47.4% of the seizure-affected pregnancies generalized tonic–clonic seizures had occurred. Various characteristics of the 418 pregnancies in which seizures occurred are compared with those for the 423 seizure-free pregnancies in Table 1. The seizure-affected pregnancies occurred in slightly younger mothers with earlier onset, longer duration seizure disorders that had substantially shorter seizure-free periods before pregnancy were more likely to be taking more than one AED and to have been made aware of the Register by a neurologist. They were more likely to have partial rather than primary generalized epilepsies. There were also differences in the outcomes of the seizures during and seizure-free pregnancies (Table 2). Those with seizures during pregnancy were more likely to experience seizures during labor and postpartum. Their risks of fetal malformation and stillbirth were not statistically significantly higher.

A comparison relating seizure control in the year prior to pregnancy to control during pregnancy indicated that 75.2% of the 391 pregnancies in WWE with seizures in the prepregnancy year had seizures during pregnancy and labor. In contrast, 19.8% of the 450 pregnancies in WWE who were seizure-free in the year prior to pregnancy, suffered seizures in pregnancy. Those with at least 1 year of seizure freedom before pregnancy more often had primary generalized epilepsies (51.8% vs. 38.6%: $p < 0.01$) and less often had partial epilepsies (42.2% vs. 55.8%: $p < 0.01$), but there were no statistically significant differences between the mean maternal ages, ages at onset of epilepsy or durations of epilepsy between the two groups.

Chances of having seizures during pregnancy appeared substantially less once there had been freedom from seizures for a year before pregnancy. The risk was 24.9% with at least 1 year of prepregnancy seizure freedom, 22.8% with at least 2 years freedom, 20.5% with at least 3 years freedom and 20% with 4 or more years of freedom. When the risk of seizures during pregnancy was plotted against duration of prepregnancy freedom from all seizures and from convulsive seizures, there appeared to be a mono-exponential decay in the risk with time till a relatively stable degree of background risk applied (Fig. 1). The durations of prepregnancy seizure freedom associated with serial halving of the risk of seizures during pregnancy were calculated to be around 7.3 months for all seizures, and 6.6 months for bilateral convulsive seizures, until baseline risks of around 16% and 8% respectively were reached.

Discussion

As Zahn et al. (1998) pointed out, the earlier literature on epileptic seizures in pregnancy is difficult to assess. It

Table 2. Various outcomes of the 418 pregnancies that had seizures during, compared with the same outcomes in the 423 pregnancies that were seizure-free. Figures are percentages

Outcome	Seizures-during	Seizure-free	Relative risk	95% C.I.	p value
Seizures during labor	4.78	0.24	22.40	3.03, 165	<0.01
Seizures during puerperium	29.90	6.38	4.69	3.16, 6.94	<0.01
Female offspring	50.62	49.65	1.02	0.89, 1.17	N.S.
Offspring with birth defect	6.46	4.02	1.61	0.89, 2.90	N.S.
Stillborn offspring	1.20	1.18	1.01	0.54, 1.88	N.S

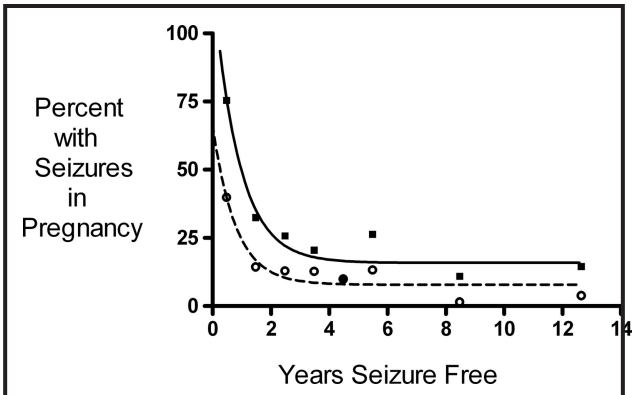

Figure 1.
Mono-exponential regressions relating percentage of AED-treated pregnancies in which seizures occurred during pregnancy to the period of seizure freedom before pregnancy for any epileptic seizures (solid squares and continuous line) and for generalized convulsive seizures (open circles and broken line). The regressions are, respectively: $\% = 15.92 + 119.5\ e^{-1.132.\text{years}}$ [$r^2 = 0.9356$. df = 5], and $\% = 7.87 + 66.9\ e^{-1.269.\text{years}}$ [$r^2 = 0.8754$, df = 5].
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is sometimes not clear how representative the populations studied were, how seizure numbers in the individual were determined, whether the seizures were generalized convulsive ones only, and whether the potential confounding effects of inadequate therapy and maternal noncompliance were considered. The series analyzed here is not necessarily representative of pregnant Australian WWE, since recruitment was voluntary and therefore open to the possibility of self-selection and other unavoidable selection biases. The accuracy of its data ultimately depended on patient testimony. Nonepileptic seizures could not be excluded with certainty. Compliance with prescribed treatment had to be assumed. It was practicable to assess only the presence or absence of known seizures, and of generalized convulsive seizures, rather than their number. However, in contemporary Australian society, the presence of any seizure rather than the actual number of seizures often determines the social handicap arising from epilepsy, especially related to driving, employment, restrictions on alcohol intake, and stigma related to widely held prejudices. Therefore freedom from seizures of all types was considered more important than freedom from generalized convulsive seizures, though data were provided for the latter as they seem to have been the only type of seizure considered in some earlier publications on epilepsy in pregnancy. One important limitation of the data is that information on prepregnancy seizure frequency had to be obtained retrospectively.

In terms of the measures studied, the epileptic process seemed to become "better" no less often than it became "worse" during pregnancy. This conclusion is based on a comparison of events during 9 months of pregnancy with events during 12 months before pregnancy. The same interpretation may not have applied if accurate counts of seizure numbers had been available. The presence or absence of any seizures may be a more robust measure of the true behavior of seizure disorders in pregnancy than patient-conducted seizure counts, or patients' impressions of whether their seizure frequencies had altered. Our figures correspond closely to recent published observations on improvement or deterioration in seizure control during pregnancy (EURAP Study Group, 2006.)

Not surprisingly, the various factors found associated with seizure occurrence during pregnancy, childbirth, and the postpartum period appear related to the presence of more difficult-to-control seizure disorders prior to pregnancy, with the difficulty in control continuing during and after pregnancy. The chances of seizures occurring during labor appeared almost negligible in seizure-free pregnancies. This knowledge may be reassuring to those who manage the deliveries of WWE. The previously reported association between altered seizure disorder behavior and longer duration of maternal epilepsy (Ramillard et al., 1982) was confirmed, but the association between seizures in pregnancy and male fetal sex (Muskens, 1928; Knight & Rhind, 1975), was not found.

From a practical standpoint, the most significant finding of the study was the relationship between duration of seizure freedom before pregnancy and the chances of being seizure-free during and after pregnancy. The risk of seizures in pregnancy was reduced by 50% to 70% once there had been 1 year's freedom from seizures before pregnancy. There was relatively little further reduction in risk with longer periods of seizure freedom, there being a seemingly ongoing background rate of seizure recurrence in pregnancy unrelated to the duration of prepregnancy seizure freedom. This apparent background rate of seizure recurrence may represent an ongoing but seemingly clinically unapparent epileptic process, but could also represent a failure to recognize, or to acknowledge, clinical epileptic phenomena when they have occurred. The relation between seizure disorder behavior in pregnancy and prepregnancy seizure activity suggests that, all other things being equal, once there has been 1 year's freedom from seizures, there appears little further advantage in deferring pregnancy to avoid seizures returning during pregnancy.

ACKNOWLEDGMENTS

Support of the Register from colleagues, the Register Advisory Board, the Epilepsy Society of Australia, Epilepsy Action, the Victorian Epilepsy Foundation, and pharmaceutical companies Sanofi-Aventis, Janssen-Cilag, Novartis, Glaxo Smith Kline, Mayne Pharma, UCB, Pfizer, and Biogen, is gratefully acknowledged.

"We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines."

Conflict of Interest: There is no personal conflict of interest by any of the authors of this paper.

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