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The outcomes of pregnancy in women with untreated epilepsy

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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).
Method: 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.
Conclusion: 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.

1. 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.

2. Materials and methods

2.1. 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,

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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.

2.2. 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).

3. 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

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[a]	−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[a]	−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[b]	3.4%		4.5%	0.74	0.30, 1.84
Malformed foetus[c]	3.4%	<	12.1%	0.28	0.11, 0.68

[a] A difference, not a R.R. value.
[b] Pregnancies exposed to VPA and TPM excluded.
[c] Pregnancies exposed to VPA or TPM.