Author/s:
Vajda, FJE;O'Brien, TJ;Graham, JE;Hitchcock, AA;Lander, CM;Eadie, MJ

Title:
Pregnancy outcomes in women with surgically treated epilepsy

Date:
2021-11-01

Citation:
Vajda, F. J. E., O'Brien, T. J., Graham, J. E., Hitchcock, A. A., Lander, C. M. & Eadie, M. J. (2021). Pregnancy outcomes in women with surgically treated epilepsy. Acta Neurologica Scandinavica, 144 (5), pp.473-477. https://doi.org/10.1111/ane.13499.

PROF. FRANK VAJDA (Orcid ID : 0000-0001-5570-7538)

MS. JANET E GRAHAM (Orcid ID : 0000-0003-2140-2351)

Article type : Original Article

PREGNANCY OUTCOMES IN WOMEN WITH SURGICALLY-TREATED EPILEPSY

FJE Vajda [ab], TJ O'Brien [b], JE Graham [a], AA Hitchcock [a], CM Lander [c], MJ Eadie [c]

a. Department of Medicine and Neurosciences, Royal Melbourne Hospital and University of Melbourne, Parkville, Victoria, Australia 3050

b.Department of Neurology, Alfred Hospital & Department of Neuroscience, Monash University, Commercial Road, Melbourne 3004, Australia

c. Royal Brisbane and Women's Hospital and School of Medicine and Biomedical Science, University of Queensland, Brisbane, Queensland, Australia 4027

Corresponding Author:
Professor Frank J.E. 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

Words: Main text 1789; Summary 144; References 169; Tables 3.

Abstract

Objective:

To ascertain whether epileptic seizure control during pregnancy differed between Australian women with previously surgically-treated epilepsy, and those with only medically-treated, epilepsy.

Materials/Methods:

Analysis of data for 74 pregnancies of women with surgically-treated focal epilepsy, compared with that from 1013 pregnancies in women with medically-treated focal epilepsy, both groups drawn from the Australian Register of Antiepileptic Drugs in Pregnancy between 1999 and 2020.

Results:

Seizures of all types, and also convulsive seizures, were less well controlled during pregnancy in the previously surgically-treated cases, the difference for seizures of all types (68.9% versus 50.1%) being statistically significant ($P < 0.05$). This result was contrary to the outcome of a previously published study of the same question carried out in India.

Conclusions:

At present, it may be premature to conclude that previous epilepsy surgery will be associated with a better chance of seizure-free, or seizure-controlled, pregnancy.

Key words: antiepileptic drugs, epilepsy, pregnancy, seizure, surgery.

Running Title: Pregnancies from surgically-treated epilepsy

Introduction

There has been a long-standing interest in the effects of pregnancy on seizure control in women with epilepsy, but the possible effects of previous and simultaneous antiepileptic drug (AED) therapy have tended to confound the interpretation of the various findings. Little information regarding the possible effects of previous epilepsy surgery had been available until 2020, when Kandraju et al. analysed data from the Kerala Registry of Epilepsy in Pregnancy in India concerning the outcome of pregnancy in women with antiepileptic drug (AED) refractory epilepsy that had been treated by surgery. They compared the outcomes of their surgically-treated pregnancies in women with epilepsy (WWE) with an age-matched control group of women whose epilepsy had been managed with medical-treatment only, and found that seizures were less likely to increase during pregnancy, as compared with the month before pregnancy, in their surgically-treated women.

We here report an analysis of data from the Raoul Wallenberg Australian Register of Antiepileptic Drugs in Pregnancy (APR), with the intention of assessing the outcomes, particularly in relation to seizure control during pregnancy, that applied for Australian women with previously surgically-treated epilepsy, in comparison with their medically-treated counterparts.

Materials and Methods

Details of the APR, which has existed since 1999, including its recruitment, data recording and ethics oversight aspects have been published previously 2,3. Information regarding the health, pregnancies, epileptic seizure disorders and their management are recorded in the APR for unselected WWE who voluntarily enrol in the Australian register. This information

is stored in a database from which relevant portions are extracted into a spreadsheet for further analysis.

The APR has been under the ethics oversight of various Melbourne based institutional human ethics committees, with that of the Melbourne Health (The Royal Melbourne Hospital) currently holding the responsibility.

For the present study, the outcomes of pregnancy in 74 pregnancies in the 59 women who had previously undergone surgery to improve the control of focal seizures that had proved refractory to AED therapy were analysed and then compared with the outcomes in the remaining 1013 pregnancies in women whose focal epilepsies had been managed with medication only. Women with brain lesions which in their own right required surgery, even though they had focal epilepsy, were excluded from the study. It was not possible to base seizure occurrence records on seizure diaries since the women involved in the study rarely keep such diaries before being enrolled in the APR. Therefore, the occurrence of any seizures before pregnancy, and at any stage during pregnancy, were the criteria utilised as measures of the presence or absence of seizure control in the two groups of women compared.

Data were analysed by univariate statistical and confidence interval analysis [2] techniques, reporting unadjusted odds ratios and taking a $P<0.05$ value as statistically significant. The logistic regression calculation employed the Stats Direct version 3.3.5 software.

Results

The majority (81%) of the operations in the 57 surgically-treated WWE in the APR were temporal lobectomies (48 instances - 14 right-sided, 17 left-sided, 17 side not recorded). Another 6 women had been operated on to remove what they referred to as ‘brain scars’ whose sites were not specified in the APR records, a further 2 for removal of frontal lobe abnormalities, and one each for parietal and occipital lobe epileptogenic foci. There was an additional lesionectomy without the site recorded.

Obstetric aspects

Details of the pregnancies studied, and their obstetric outcomes, are set out in Table 1.The only statistically significant differences between those of the surgically-treated and the non-surgically-treated women were that: a higher proportion of the former had been enrolled in

the APR before 20 weeks of pregnancy, more often had family histories of foetal malformations, and had pregnancies that culminating in premature births.

Epilepsy aspects

Table 2 lists the AEDs that were employed in the earlier part of pregnancy in the women studied, and provides details of aspects of the focal epilepsies that were involved and of the control of seizures (of any type, and convulsive seizures only) before and during pregnancy, and in the post-partum period. Compared with the only medically treated women's pregnancies in the APR, the statistically significant differences found were that, in the surgically-treated women's pregnancies (i) epilepsy had tended to begin at an earlier age, and had been present for longer before their entry into the APR (ii) that AED monotherapy was less often used (iii) that frequencies of prescription of the more commonly used AEDs differed and (iv) that seizure-free pre-pregnancy years, seizure-free pregnancies and seizure-free post-partum periods were all less frequent. There also were lower rates of convulsive seizure freedom in the corresponding pregnancy stages, though not statistically significantly so. Seizures recurred during pregnancy in 9 of the 30 pregnancies in women with surgically-treated epilepsy (30.0%) who had been seizure-free in their pre-pregnancy year. The corresponding rate was 123 in 541 (22.7%) in the not-surgically-treated women with focal epilepsy (O.R. = 1.456; 95% C.I. 0.6503, 3.2620).

Certain potentially relevant aspects of the surgically-treated women's pregnancies in the Kerala and Australian data are compared in Table 3. There were differences between certain epilepsy-related and also obstetric aspects of the post-surgery pregnancies between the Kerala and Australian registers. In the Kerala material, seizures increased more often during pregnancy in the non-surgically managed women than in the post-surgery ones (39.6% versus 14.9%, P=0.001): in the APR data, there was a trend for seizure control to be more often lost during pregnancy in the post-surgery women's pregnancies than in the non-surgically managed ones (30.0% versus 22.7%; O.R. 1.4564, 95% C.I. 0.6503, 3.2620). There was greater prescription of AED combinations and employment of the more recently available AEDs, particularly lamotrigine and levetiracetam, in the APR material, in which there was no recorded use of phenobarbital, unlike the Kerala material. The seizure disorders also tended to have begun later in life in the APR series. A logistic regression analysis showed that the only factor that probably influenced seizure occurrence during pregnancy in the APR data was the duration of pre-pregnancy seizure control (P = 0.0009, with the cut-off P value being

P=0.0125, after applying Bonaferroni's correction). There appeared to be no clearly interpretable data for this parameter in the Kerala published material.

Discussion

In many respects the surgically- and non-surgically treated women's pregnancies in the APR appeared reasonably similar in relation to what might be regarded as their obstetric aspects and outcomes, though there was a higher incidence of premature births in the previously surgically-treated women. From the epilepsy point of view, the members of the surgically-treated group had earlier onsets of epilepsy, longer durations of existence of seizure disorders, were less likely to be treated with AED monotherapy, and had less adequately controlled seizure disorders before, during, and after pregnancy. This lesser degree of seizure disorder control may account for the greater use of AED polytherapy in the APR surgically-treated group, consistent with this patient group overall having more severe epilepsy.

In comparing the APR with the Kerala pregnancies, different local social circumstances and obstetric practices may account for the women in the latter group tending to be younger, to more often be carrying first babies, and to have undergone Caesarean section rather more often. That mode of delivery may have contributed to the higher incidences of premature and low birth weight babies in the Kerala material, as compared with the APR pregnancies.

In the APR material, the seizure-affected pregnancy rate was higher in the surgically-treated women's pregnancies than in the comparison focal epilepsy pregnancies: in the Kerala surgical pregnancies seizure control was better than in the comparison pregnancies of the non-surgically managed women. Seizure control was measured in somewhat different ways in the two registers. The measure used for the APR data was the presence or absence of any seizures over periods of time before, throughout and after pregnancy, the pre-pregnancy period being one year in duration. In general, in Australia freedom from all seizures for a year enables a woman to drive a motor vehicle legally, and not to be able to do this usually imposes a major limitation on her way of life. In the Kerala register data, it appears that any increase over the pre-pregnancy-month seizure count in any one-month's seizure count during pregnancy was regarded as the measure of seizure control worsening. This difference between the two registers in methods of assessing seizure control make comparison of this aspect of their findings somewhat uncertain. However, it hardly seems sufficient to explain the essentially contrary findings in regards to seizure control during the pregnancies of the two sets of women with surgically-treated epilepsy.

The nature of the AEDs prescribed for women in the two registers differed, on the whole there being greater use of more recently introduced AEDs in the Australian women. It is impossible to know what contribution this difference may have made to the different behaviours of the seizure disorders during pregnancy when, for instance, no information is available about differences in patient compliance or prescriber therapeutic skills and management practices. Previous studies from both the APR and the Kerala register, and other investigations, have shown that pre-pregnancy seizure freedom, i.e. full seizure control, correlates with decreased risk of seizures during pregnancy 4-6. In the APR data, seizure-affected pregnancy rates were statistically significantly higher in the surgically-treated women than in the comparison pregnancies: in the Kerala data the mean seizure occurrence rate appears to have been 1.7 times higher in the comparison non-surgically-treated women's pregnancies than in the surgically treated women's.

However, probably because of the very wide standard deviation quoted in what was presumably untransformed data, this difference in rates seems not to have been statistically significant. These different seizure control rates before pregnancy between the previously surgically-treated and comparison women's pregnancies in the data from the two Registers may have made a significant contribution to the different behaviours in relation to seizure control during pregnancy in the two sets of surgically-treated women.

Until larger data sets become available, the above analysis suggests that it may be premature to conclude that previous epilepsy surgery will necessarily be associated with a better chance for a subsequent seizure-free, or seizure- well-controlled, pregnancy, a highly desirable outcome though that be.

References

1 Kandraju SS, Jose M, Salini RA, et al. Women with drug-resistant epilepsy: Surgery or pregnancy first? Epilepsia. 2020; 61: 1758-1763.

2 https://pedro.org.au/english/resources/confidence-interval-calculator/

3 Vajda FJ, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. The Australian Register of Antiepileptic Drugs in Pregnancy: the first 1002 pregnancies. Aust N Z J Obstet Gynaecol. 2007; 47: 468-474.

4 Vajda FJ. The Australian Pregnancy Register of Anti-epileptic Drugs: 10 years of progress. *J Clin Neurosci.* 2010; 17: 1485-1488.

5 Vajda FJ, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. Seizure control in antiepileptic drug-treated pregnancy. Epilepsia. 2008; 49: 172-176.

6 Harden CL, Hopp J, Ting TY, et al. Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2009; 50:1229-1236.

7 Thomas SV, Syam U, Devi JS. Predictors of seizures during pregnancy in women with epilepsy. Epilepsia. 2012; 53: e85-e88.

Acknowledgements:

We acknowledge the help provided by professional and lay colleagues who referred patients to the Australian Pregnancy Register (APR), and wish to thank the Scientific Advisory Board and the Ethical Research Committees of St. Vincent's Hospital, Monash Medical Centre, the Royal Melbourne Hospital, and other institutions for their continuing ethics oversight of the APR. The Register is grateful for support from the Epilepsy Society of Australia, The Royal Melbourne Hospital Neuroscience Foundation, Epilepsy Action, and financial assistance from the National Health and Medical Research Council, and the pharmaceutical companies Sanofi-Aventis, Genzyme, UCB Pharma, Sci-Gen, and Eisai.

Conflicts of Interest:

FJE Vajda has received research support for the Australian Pregnancy Register from the Epilepsy Society of Australia, NHMRC, RMH Neuroscience Foundation, Epilepsy Action, Sanofi-Aventis, Eisai, UCB Pharma, and Sci-Gen. T O'Brien has received research support from the Epilepsy Society of Australia, NHMRC, RMH Neuroscience Foundation, Sanofi-Aventis, UCB Pharma, and Sci-Gen and Eisai. JE Graham, AA Hitchcock, CM Lander, and MJ Eadie have no relevant conflicts of interest to declare.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Table 1. Details of the two APR groups of pregnancies compared, and their obstetric outcomes. Denominators for ratios are shown only when they differ from the column totals shown in the headings.

	NO SURGERY N = 1013		**SURGERY** N = 74		**Differs by**	**95% C.I.**
Maternal age (years)	31.26 ± 4.51		31.39 ± 5.19		0.13	-0.33, 0.59
Pregnancy details		**%**		**%**	**Odds Ratio**	
Neurologist involved	498	49.2	39	52.7	1.152	0.718, 1.849
Other APR pregnancies	424	41.9	35	47.3	1.247	0.777, 2.001
Enrolled before 20 weeks	483/964	50.1	46/72	63.9	1.762	1.02, 2.897
Assisted fertilisation	71	7.0	3/72	4.2	0.577	0.177, 1.879
IVF	41	4.1	2/72	2.8	0.677	0.162, 2.859
F H epilepsy	279	27.5	17	23.0	0.785	0.449, 1.372
F H malformations	144	14.2	19	25.7	2.085	1.202, 3.615
Primigravida	400	39.5	28	37.8	0.933	0.574, 1.517
Outcomes						
Pre-37 weeks birth	52/954	5.5	8/70	11.4	2.238	1.018, 4.920
Twins	21	2.1	1	1.4	0.647	0.086, 4.879
Live normal infant	915	90.3	67	90.5	1.025	0.460, 2.295
Spontaneous abortion	28	2.8	1	1.4	0.482	0.065, 3.592
Stillborn	11	1.1	2	2.7	2.530	0.550, 11.633
Birth weight < 2.5kg	60/898	6.7	8/70	11.4	1.802	0.825, 3.937
Malformed foetus	61/976	6.3	6/72	8.3	1.364	0.568, 3271
Caesarean birth	362/960	37.7	29/70	41.4	1.168	0.714, 1.913

Table 2. Comparison of aspects related to epilepsy in the pregnancies of surgically and non-surgically treated women with focal epilepsies in the APR. Denominators for ratios are included only when they differ from column totals shown in the heading rows.

	NO SURGERY		**SURGERY**			
	N = 1013		N = 74		**Differs by**	**95% C.I.**
Epilepsy onset age (yrs.)	18.97 ± 8.59		12.63 ± 8.19		6.34	4.30, 8.38
Epilepsy duration (yrs.)	12.41 ± 8.55		18.93 ± 7.99		6.52	4.51, 8.53
Seizure-free years	2.21 ± 3.63		1.51 ± 2.61		0.70	P=0.104[$]
AED Therapy		**%**		**%**	**Odds Ratio**	
At outset of pregnancy.	940	92.8	65	87.8	0.561	0.269, 1.172
Changed before pregnancy	147	15.6	9	12.9	0.796	0.387, 1.640
Changed in pregnancy.	348	34.4	25	33.8	0.975	0.592, 1.606
Monotherapy	683/940	67.9	32/65	49.2	0.459	0.277, 0.761
AED in early pregnancy	N = 939		N = 65			
Carbamazepine (CBZ)	391	41.6	35	53.9	1.635	0.987, 2.705
Valproate (VPA)	97	16.3	2	3.1	0.276	0.066, 1.144
Lamotrigine (LTG)	328	34.9	19	29.2	0.769	0.443, 1.335
Levetiracetam (LEV)	164	17.5	20	30.8	2.100	1.208, 3.651
Topiramate (TPM)	71	7.6	12	18.5	2.768	1.414, 5.418
Phenytoin (PHT)	50	5.3	3	4.6	0.860	0.261, 2.837
Clonazepam (CZP)	47	5.0	6	9.2	1.930	0.793, 4.698
Seizure occurrence						
Pre-pregnancy year	472	46.6	44	59.5	1.681	1.040, 2.717
During pregnancy	507	50.1	51	68.9	2.213	1.332, 3.676
During labour	29/946	3.1	0/70	0	P=0.253#	
In post-partum period	188/947	19.9	27/70	38.6	2.535	1.527, 4.209
Lost control in pregnancy	123/541	22.7	9/30	30.0	1.456	0.650, 3.262
Convulsive seizures						
Pre-pregnancy year	150	14. 8	14	18.9	1.342	0.732, 2.43

During pregnancy	210	20.7	18	24.4	1.29	0.708, 2.135
During labour	10/1012	1.0	0/73	0	P>0.999 #	
In post-partum period	55	5.4	5/72	6.9	1.300	0.504, 4.356

$ 't' test: # Fisher's exact test

Table 3. Comparison of various items relating to pregnancies in women with surgically-treated focal epilepsy from the Kerala and from the APR data sets.

	Kerala series (N=67)	**APR series (N=74)**
Epilepsy related aspects		
Seizures increased /control lost in pregnancy	14.9%	30.0%
Mean epilepsy onset age (years)	9.8	12.6
Mean epilepsy duration (years)	17.4	18.9
No AEDs in early pregnancy	14.9 %	12.2 %
AED monotherapy	70.8 %	49.2 %
AED in mono- and poly-therapy		
Carbamazepine intake	64.2 %	47.3 %
Clobazam intake	14.9 %	0
Clonazepam intake	0	8.1 %
Lamotrigine intake	0	25.7 %
Levetiracetam intake	3.0 %	27.0 %
Oxcarbazepine intake	6.0 %	0
Phenobarbitone intake	7.5 %	0
Phenytoin intake	7.5 %	4.1 %
Topiramate intake	3.0 %	16.2 %
Valproate intake	7.5 %	2.7 %
Obstetric related aspects		
Mean maternal age (years)	27.4	31.4
First pregnancy	80.6 %	37.8 %
Pre-term birth	24.6 5	11.4 %

Caesarean section	48.3 %	41.4 %
Low birth weight	38.1 %	11.4 5
Fetal malformation	8.1 %	8.3%