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

Title:
Seizure control in successive pregnancies in Australian women with epilepsy

Date:
2022-11-01

Citation:
Vajda, F. J. E., O'Brien, T. J., Graham, J., Hitchcock, A. A., Perucca, P., Lander, C. M. & Eadie, M. J. (2022). Seizure control in successive pregnancies in Australian women with epilepsy. Acta Neurologica Scandinavica, 146 (5), pp.610-614. https://doi.org/10.1111/ane.13688.

Persistent Link:
https://hdl.handle.net/11343/327245

Received: 10 June 2022 | Revised: 2 August 2022 | Accepted: 7 August 2022

DOI: 10.1111/ane.13688

Acta Neurologica Scandinavica WILEY

ORIGINAL ARTICLE

Seizure control in successive pregnancies in Australian women with epilepsy

Frank J. E. Vajda[1,2] | Terence J. O'Brien[2,3] | Janet Graham[1] | Alison A. Hitchcock[1] | Piero Perucca[1,2,3,4,5] | Cecilie M. Lander[6] | Mervyn J. Eadie[6]

[1]Departments of Medicine and Neurosciences, The Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia

[2]Department of Neuroscience, Monash University, Melbourne, Victoria, Australia

[3]Department of Neurology, Alfred Health, Melbourne, Victoria, Australia

[4]Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia

[5]Comprehensive Epilepsy Program, Austin Health, Heidelberg, Victoria, Australia

[6]Royal Brisbane and Women's Hospital and School of Medicine and Biomedical Science, University of Queensland, Brisbane, Queensland, Australia

Correspondence
Frank J. E. Vajda, Department of Medicine and Neurosciences, Royal Melbourne Hospital and University of Melbourne, Parkville 3050, Vic., Australia.
Email: vajda@netspace.net.au

Funding information
Eisai; Epilepsy Action Australia; Epilepsy Society of Australia; UCB Pharma

Objectives: To investigate control of epileptic seizures during pairs of successive pregnancies in antiseizure medication (ASM)-treated women with epilepsy.

Materials and Methods: Analysis of seizure freedom rates during 436 pairs of successive pregnancies in Australian women with epilepsy, in nearly all instances long-standing epilepsy.

Result: There was a higher rate of seizure-free second pregnancies compared with first paired pregnancies (63.1% vs. 51.4%; Relative Risk (R.R.) = 1.2277; 95% CI 1.0930, 1.3789) and of seizure-free pre-pregnancy years before second as compared with first paired pregnancies in the same women (63.6% vs. 52.4%; R.R. = 1.2616; 95% CI 1.1337, 1.4040). In 108 women whose ASM therapy was unaltered throughout both of their pregnancies, the seizure-freedom rate was higher in the second of the paired pregnancies (82.4% vs. 69.4%; R.R. = 1.1867, 95% CI 1.0189, 1.3821).

Conclusions: Altered ASM therapy after the first of a pair of successive pregnancies did not fully account for the better overall seizure control in the corresponding second pregnancies. Some additional factor may have been in operation, possibly a greater preparedness to undertake a further pregnancy if seizures were already fully controlled.

KEYWORDS
antiseizure medication, epilepsy, pregnancy, seizure freedom, successive pregnancies

1 | INTRODUCTION

There has been a long-standing medical interest in the possible effects of pregnancy on the course of epileptic seizure disorders. In earlier times, it has been generally appreciated that the available data were derived from mainly ASM-treated pregnancies, but the consequences for seizure control of the frequent tendency of ASM clearance to increase during pregnancy[1] were often not recognized. More recently, the matter of ASM-related teratogenesis has increasingly claimed the interest of those working in the area of epilepsy and pregnancy, and has tended to divert attention from the matter of seizure control in pregnancy. In regard to the latter, the focus of interest has usually tended to lie in what has happened in the individual pregnancy rather than in what happened to seizure control throughout the series of pregnancies that may have occurred during the reproductive life of the individual woman with epilepsy. The present paper attempts to explore the latter issue in successive pregnancies of Australian women with epilepsy (WWE), utilizing data from pairs of consecutive pregnancies recorded in the Raoul Wallenberg Australian Register of Epileptic Drugs in Pregnancy (APR). It supplements a previous account of seizure control in individual pregnancies of WWE from the same dataset.[2]

2 | MATERIALS AND METHODS

2.1 | The APR

This study is based on data concerning the pregnancies of WWE that were recorded in the APR between 1999 and 2021. Details of this Register, its policies and practices concerning data collection have been published.[3,4] Inclusion of women in the APR database has been voluntary. If women became aware of the Register's existence and were planning pregnancy, or were already pregnant, they chose whether or not to be included in the APR database, which has been estimated to contain information on about 8.7% of the relevant pregnancies occurring in Australia.[5] Contact between enrolled pregnant women and the APR staff has always been via telephone. Data concerning each woman's medical details and pre-pregnancy epilepsy situation and the course of her pregnancy were recorded (i) at enrolment, (ii) at approximately 28 weeks of pregnancy, (iii) whenever possible within the first post-partum month, or, if not, as soon afterwards as feasible. The accuracy of the information provided was checked with the women's treating medical practitioners, whenever practicable, and the clinical management of the women always remained in the hands of these practitioners. Over the years, the APR has been under the oversight of various Melbourne-based institutional Human Ethics Research Committees, currently that of Melbourne Health. All women enrolled have provided written informed consent for participation.

The women involved had not kept seizure diary records before enrolling in the APR, and it proved impracticable for them to keep such diaries throughout the duration of their pregnancies. Therefore, seizure activity was recorded in terms of being present or absent (i) before and (ii) during pregnancy. Any recognizable epileptic event, and not merely a convulsive one, was considered a seizure.

2.2 | Data analysis

Potentially relevant items of information were extracted from the APR database into an Excel spreadsheet, and then analysed by simple statistical methods and confidence interval techniques, or by multivariate logistic regressions employing Stats Direct software. p values <.05, after adjustment where necessary for multiple comparisons using Bonferroni's method, were considered statistically significant.

3 | RESULTS

3.1 | The pregnancies studied

After exclusion of women in whom either of a pair of successive pregnancies had ended in spontaneous abortion (the shorter duration of such pregnancies would favour the chance of them being seizure-free), there were available for analysis paired completed pregnancies (designated as P1 and P2 for the purposes of present analysis) in 436 women. The mean age of these women at the times of their P1 pregnancies was 29.74 ± 3.90 years, the mean interval between the two pregnancies 2.62 ± 1.81 years the median value of the inter-pregnancy interval being 2 years. The mean duration of the women's epilepsies at the time of the P1 pregnancies was 12.8 ± 7.6 years, being shorter than 2 years in only 3.7% of the women, and shorter than 3 years in 9.9%. The type of epilepsy suffered had been classed as focal in 49.3% of the women, as generalized in 45.6%, and as uncertain in the remainder. Neurologists had referred 64.4% of the P1 pregnancies to the APR, the women involved often being self-referred in their next pregnancy.

3.2 | Factors relevant to seizure control

To identify items recorded in the APR which seemed potentially relevant to seizure control in the pregnancies, multiple variable logistic regressions were fitted separately to P1 and P2 pregnancies for seizure freedom on maternal age, age at onset of epilepsy, duration of epilepsy, seizure freedom for over a year before pregnancy, whether the epilepsy was focal or generalized, whether ASMs were taken in the earlier part of pregnancy, and on dosages of carbamazepine, valproate, lamotrigine, levetiracetam, topiramate, phenytoin and clonazepam, the most commonly used ASMs. Based on P values, individual covariates unlikely to be relevant were then stripped progressively from repeated regression analyses until the regressions became statistically significant, the statistically significant covariates that emerged then being studied further. Without presenting the detailed data here, the relevant covariates were (i) being seizure-free for more than a year before pregnancy (p value <.0001 for both the P1 and P2 regressions) and (ii) lamotrigine dosage (p < .05 for the P1 regression).

Seizure freedom before pregnancy and ASM dosage were therefore taken into consideration in the further analyses, but before doing that the possible consequences of time-related changes in treatment practice over the two decades of the APR's existence were assessed.

3.3 | Effects of year of pregnancy

The 436 P1 pregnancies were divided into two sets, those occurring prior to 2007 (N = 234), and those beginning in that year, or later (N = 202). Seizure-free P1 pregnancies had occurred in 51.5% of the earlier group and 51.3% of the latter group of pregnancies. The corresponding figures for the P2 pregnancies of the same women, after subdivision of the group into those occurring before and after the end of 2009 (N = 208 and 238, respectively), were 61.5% and 64.5% (Relative Risk (R.R.) = 1.0477, 95% CI 0.9069, 1.2103).

It therefore seemed that the year when pregnancy occurred was unlikely to play any major confounding role in relation to interpreting seizure control rates in the P1 or the P2 pregnancies.

3.4 | Seizure control, P1 versus P2

Seizure freedom had been present throughout 224 of the 436 P1 pregnancies (51.4%), and throughout 275 (63.1%) of the P2 ones in the same women (R.R. = 1.2277; 95% CI 1.0930, 1.3789). This higher rate of full seizure control throughout the P2 pregnancies correlated with the fact that, while 193 of the women (44.3%) were seizure-free in both their pregnancies and 130 (19.8%) had both pregnancies seizure-affected, only 31 (7.1%) had a seizure-affected P2 pregnancy after a seizure-free P1 pregnancy, but 82 (18.8%) had a seizure-free P2 pregnancy after a seizure-affected P1 pregnancy (R.R. = 2.6452; 95% CI 1.7855, 3.9121).

3.5 | Pre-pregnancy seizure freedom

The pre-pregnancy year had been seizure-free in 237 of the 436 P1 pregnancies (54.4%) and in 289 (63.6%) P2 ones (R.R. = 1.2616; 95% CI 1.1337, 1.4040), a difference paralleling the different rates of seizure freedom between P1 and P2 pregnancies. Seizure freedom throughout pregnancy and seizure freedom in the pre-pregnancy year had been highly correlated in the above-mentioned logistic regression analyses.

3.6 | ASM dosage

Before pregnancy, ASMs and/or ASM dosages had been changed in 97 of the 436 P1 pregnancies and in 54 of the P2 pregnancies in the same women. Valproate was the drug mainly involved in the changes, its intake being ceased in 38 of the P1 pregnancies and its dose reduced in another 12, though the dose had been increased in four. In the 54 P2 pregnancies where there were pre-pregnancy ASM treatment changes, valproate again was the main drug involved. Its intake had been ceased in 15 of these pregnancies, and its dose reduced in another 10.

The extents of use and mean dosages of the more commonly employed ASMs in the earlier parts of the P1 and P2 pregnancies are set down in Table 1. Between the dates of successive pregnancies, there had been decreased use of the older ASMs, particularly CBZ and VPA, with mean lower dosage of the latter. However, there had been increased use, and use in higher mean dosages, of the newer agents LTG and LEV.

There had also been various alterations in the natures of the other ASMs prescribed, and in their dosages, during the courses of some individual pregnancies as they progressed into their later months. Such changes had occurred in 32.8% of P1 and in 28.4% of P2 pregnancies. Thus, ASM therapy had remained unaltered throughout pregnancy in the majority of pregnancies. The stage of pregnancy when the alterations were made varied considerably between individual pregnancies, but its mean value was at 23.5 weeks of pregnancy. The variety and extents of the changes are too varied for simplicity of description, though the changes mainly involved increased ASM dosages rather than change in ASM. It was sometimes recorded that the dosage increases had been made in response to plasma ASM concentration values, though that particular item of information had not been specifically sought by interviewers. Valproate intake had been resumed by the end of P1 in 8 of 38 women in whom use of the drug had been ceased before pregnancy, and in 5 of the 15 in whom its intake had been ceased before their P2 pregnancies.

TABLE 1 Numbers of the 436 women taking particular ASMs in the earlier parts of P1 and P2, and mean dosages of these drugs (mg/day)

	P1		P2	
ASM	*N*	Mean ± SD	*N*	Mean ± SD
None	33		37	
CBZ	128	677.3 ± 362.7	121	691.7 ± 362.6
VPA	93	793.5 ± 445.5	78	710. 3 ± 470.6
LTG	144	263.5 ± 157.5	148	300.8 ± 168.5
LEV	78	1734 ± 912.9	97	1817 ± 925.3
TPM	32	253.3 ± 132.8	33	229.5 ± 129.9
PHT	12	347.5 ± 137.5	10	381.0 ± 110.6
CZP	15	1.46 ± 1.94	21	1.49 ± 1.68
>1 ASM	110		121	

The higher overall seizure-freedom rates in the same women for P2 pregnancies could be attributed to the ASM changes shown in Table 1. However, it was possible to investigate the matter further by restricting consideration to seizure freedom rates in women who took the same ASMs in the same dosages in at least the earlier parts of both of their P1 and P2 pregnancies, compared with those where earlier pregnancy stage ASM regimens differed between P1 and P2 pregnancies.

3.7 | Unchanged versus changed ASM therapy

ASM therapy was unchanged between the earlier months of successive pregnancies in 190 of the women studied, but altered in nature, in dosage or in both between P1 and P2 pregnancies in the remaining 246. Details of percentages of pregnancies treated with particular ASMs, and their mean dosages, are shown in Table 2.

Where the earlier stage therapy did not differ between pregnancies, 126 (66.3%) of the 190 P1 pregnancies were seizure-free throughout, as were 155 (81.6%) of the P2 ones (R.R. = 1.2302, 95% CI 1.0891, 1.3895). Where earlier stage pregnancy ASM treatment was different between the P1 and P2 pregnancies, the corresponding figures were 98 and 135 out of 246 (39.8% vs.

TABLE 2 Comparison of percentages of women taking particular ASMs in the earlier halves of P1and P2, and mean dosages of these drugs (mg/day), for women with unchanged and changed ASM regimens in their pairs of pregnancies

	Unchanged ASMs		Changed ASMs			
	Both pregnancies $N = 190$		P1 $N = 246$		P2 $N = 246$	
ASM	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD
None	8.4	0	8.5	0	8.5	0
CBZ	31.1	655.9 ± 365.1	28.0	695.7 ± 362.4	25.2	722.6 ± 512.1
VPA	17.9	823.5 ± 389.3	24.0	776.3 ± 477.2	17.9	622.7 ± 372. 1
LTG	25.3	286.5 ± 162.1	39.0	252.0 ± 154.8	40.7	302.7 ± 172.3
LEV	20.5	1782 ± 960.0	15.9	1660 ± 872.1	23.6	1840 ± 906.9
TPM	4.7	277.8 ± 120.2	9.3	243.8 ± 139.7	9.8	211.5 ± 131.0
PHT	2.1	280.0 ± 56.0	3.3	381.3 ± 156.3	2.4	430.3 ± 107.8
CZP	4.2	2.09 ± 2.49	2.8	0.74 ± 0.66	4.9	1.22 ± 0.85
>1 ASM	21.6		28.2		32.5	

TABLE 3 Differences in various factors between P1 and P2 pregnancies managed with unchanged and changed ASM regimens in the earlier stage of both pregnancies

Factor	Unchanged $N = 190$		Changed $N = 246$		R.R.	95% CI
P1: < 1 year seizure-free	66	34.7%	133	54.1%	1.5564	1.2411, 1.9519
P2: < 1 year seizure-free	35	18.4%	102	41.5%	2.2509	1.6117, 3.1436
P1: later stage ASM change	61	32.1%	141	57.3%	1.7853	1.4139, 2.2542
P2: later stage ASM change	64	33.7%	105	42.7%	1.2671	0.9930, 1.6214
P1: later stage dose increase	51	26.8%	102	41.5%	1.5447	1.1701, 2.0393
P2: later stage dose increase	50	26.3%	82	33.3%	1.2667	0.9219, 1.7036

54.9%; R.R. = 1.3776, 95% CI 1.1382, 1.6672). Thus, there was statistically significantly better seizure control in the P2 than in the P1 pregnancies in both subsets of women. However, the fact that this was the case when there was no difference in treatment in at least the earlier halves of successive pregnancies suggested that altered ASM therapy did not account fully for the higher rate of seizure control in the P2 pregnancies in at least this particular subgroup.

Moreover. within the 190 women where earlier stage ASM treatment did not differ between paired pregnancies, there were 108 in whom ASM intake did not change in nature or drug dosage during the full durations of either pregnancy. Even in these women, seizure freedom rates were higher in P2 than in P1 pregnancies (82.4% vs. 69.4%; R.R. = 1.1867, 95% CI 1.0189, 1.3821). Hence, the higher seizure-freedom rate in P2 pregnancies still existed when possible effects of ASM changes at any stage of pregnancy were excluded.

3.8 | Differences between the subgroups

Table 3 compares certain potentially relevant factors in relation to the higher seizure freedom rates in the earlier pregnancy stage ASM-unchanged than in the earlier stage ASM-changed pregnancies. As compared with P1 pregnancies in the ASM-changed group, there was statistically significantly better seizure control before pregnancy, proportionately fewer women with ASM changes, and fewer with ASM dose increases during pregnancy, in the unchanged therapy subgroup. In P2 pregnancies, a similar finding applied for pre-pregnancy seizure freedom. However, proportions of women with ASM changes and with ASM dose increases were not statistically significantly higher in the changed subgroup. The two subgroups did not differ statistically significantly in mean durations of their epilepsies at the times of their P1 APR pregnancies (13.3 ± 7.9 and 12.4 ± 7.4 years, respectively).

4 | DISCUSSION

Three main finding have emerged from the present analysis. Firstly, the previously demonstrated strong correlation between freedom from seizures in the pre-pregnancy months or year and seizure-free pregnancy in the APR data[6,7] has again been found. It empathizes the importance of achieving sustained seizure control prior to pregnancy. It also raises the possibility that pre-pregnancy seizure control may carry over into pregnancy for an uncertain and perhaps variable period of time.

Secondly, in the population studied, which for the greater part comprised women with ASM-treated long-standing epilepsies where there should have been abundant time for optimal possible seizure control to have been achieved before pregnancy, the women involved seemed to fall into two groups. In one, what may be regarded as reasonably optimal seizure control had already been achieved before pregnancy was undertaken, so that

little further adjustment of therapy was needed, apart perhaps of employing measures to reduce the hazard of teratogenesis. In the other group, in which pre-pregnancy seizure control was less adequate, further treatment manipulation seems to have been carried out in a not entirely successful attempt to obtain better seizure control, but again often while apparently giving regard to teratogenicity issues.

Thirdly, and perhaps more interestingly and more unexpectedly, there was a consistent trend toward better seizure control in P2 than in P1 pregnancies in the same ASM-treated women. At least part of this trend appeared independent of alterations made in ASM therapy. From the available data, it was not possible to discern factors that correlated with this trend, except that the trend may possibly reflect a greater preparedness to undertake further pregnancies if seizures are fully controlled.

In considering the above findings and their interpretation, the reader should keep in mind the fact that the study comes from a comparatively wealthy Western nation with well-developed health services. Its findings are derived from data provided by a largely self-selected population of pregnant women with predominantly chronic ASM-treated epilepsies. Such women may not necessarily be fully representative of Australian women with epilepsy, let alone those in other countries. Further, the women studied have usually been under the care of neurologists, information about their seizure occurrence has been obtained retrospectively and not from contemporary seizure diaries, and their statements regarding compliance with prescribed therapy have been accepted as correct.

ACKNOWLEDGMENTS

We are grateful to professional and lay colleagues and to various bodies for referring patients to the APR, and also to the Scientific Advisory Board and the Ethical Research Committees of St. Vincent's Hospital, Monash Medical Centre, the Royal Melbourne Hospital and other relevant institutions for continuing ethics oversight of the APR. Over its years, The Epilepsy Society of Australia, The Royal Melbourne Hospital Neuroscience Foundation, Epilepsy Action Australia, the NHMRC and the pharmaceutical companies Sanofi-Aventis, UCB Pharma and Eisai and have provided financial support towards the maintenance of the APR. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

CONFLICT 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 Australia, Sanofi-Aventis, Eisai, and UCB Pharma. T O'Brien has received research support from the Epilepsy Society of Australia, NHMRC, RMH Neuroscience Foundation, Sanofi-Aventis, UCB Pharma, Sci-Gen and Eisai. P. Perucca is currently supported by the National Health and Medical Research Council (APP1163708), the Epilepsy Foundation, The University of Melbourne, Monash University, Brain Australia, and the Weary Dunlop Medical Research Foundation. He has received speaker honoraria or consultancy fees paid to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma, and is an Associate Editor for *Epilepsia Open*. JE Graham, AA Hitchcock, CM Lander and MJ Eadie have no relevant conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13688.

DATA AVAILABILITY STATEMENT

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

ORCID

Frank J. E. Vajda https://orcid.org/0000-0001-5570-7538
Janet Graham https://orcid.org/0000-0003-2140-2351

REFERENCES

1. Reisinger TL, Newman M, Loring DW, Pennell PB, Meador KJ. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. *Epilepsy Behav*. 2013;*29*(1):13-18. doi:10.1016/j.yebeh.2013.06.026
2. Vajda FJE, O'Brien TJ, Graham JE, et al. Epileptic seizure control during and after pregnancy in Australian women. *Acta Neurol Scand*. 2022;*145*(6):730-736. doi:10.1111/ane.13609
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*(6):468-474. doi:10.1111/j.1479-828X.2007.00781.x
4. Vajda FJ. The Australian pregnancy register of anti-epileptic drugs: 10 years of progress. *J Clin Neurosci*. 2010;*17*(12):1485-1488. doi:10.1016/j.jocn.2010.05.008
5. Vajda FJ, O'Brien TJ, Graham J, Lander CM, Eadie MJ. The Australian Register of Antiepileptic Drugs in Pregnancy: changes over time in the epileptic population. *J Clin Neurosci*. 2014;*21*(9):1478-1482. doi:10.1016/j.jocn.2013.11.049
6. Vajda FJ, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. Seizure control in antiepileptic drug-treated pregnancy. *Epilepsia*. 2008;*49*(1):172-176. doi:10.1111/j.1528-1167.2007.01412.x
7. 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*(5):1229-1236. doi:10.1111/j.1528-1167.2009.02128.x

How to cite this article: Vajda, F. J. E., O'Brien, T. J., Graham, J., Hitchcock, A. A., Perucca, P., Lander, C. M. & Eadie, M. J. (2022). Seizure control in successive pregnancies in Australian women with epilepsy. *Acta Neurologica Scandinavica*, *146*, 610–614. doi: 10.1111/ane.13688