PREGNANCY AFTER VALPROATE WITHDRAWAL –

FOETAL MALFORMATIONS and SEIZURE CONTROL

Frank J E Vajda [ab], Terence J O'Brien [b], Janet E Graham [a], Alison A Hitchcock [a], Cecilie M Lander [c], Mervyn J 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 FJE 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

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

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Abstract

Objective: To assess the outcomes in women with epilepsy in relation to foetal malformation and epileptic seizure control during pregnancy when valproate (VPA) intake was ceased, or the drug's dosage was reduced before pregnancy.

Methods: Statistical analysis of data collected in the Australian Pregnancy Register of between 1999 and 2018 concerning 580 pregnancies previously treated with VPA, with the VPA dosage reduced or the drug withdrawn prior to pregnancy in 158 cases.

Results: While the available data have limitations, foetal malformation rates in the pregnancies studied were lower in the VPA changed pregnancies (4.5%) than in the VPA unchanged comparator pregnancies (10.9%, H.R. = 0.412; 95% C.I. 0.190, 0.892), and were only 2.7% where VPA intake was ceased before pregnancy (H.R. = 0.262; 95% C.I. 0.083, 0.826). Seizure-affected pregnancies were more frequent in the VPA changed pregnancies than in the VPA unchanged ones (46.2% *versu*s 30.8%: H.R. = 1.500; 95% C.I. 1.203, 1.870). Convulsive seizure-affected pregnancies also were increased, but not statistically significantly so.

Significance: Pre-pregnancy reduction in VPA dosage reduced the hazard of foetal malformations, while ceasing intake of the drug decreased the hazard to one similar to that which applies in the general population, but at a cost of

decreased control of epileptic seizures during the pregnancies studied. Further investigations are needed to see whether such findings apply more widely in women with epilepsy.

Key words: foetus, epilepsy, malformations, pregnancy, seizures, valproate

Key Points:

Australian Pregnancy Register data on 580 pregnancies in WWE treated with VPA

Reduction of VPA dose, or ceasing VPA pre-pregnancy reduced risk of teratogenicity

Cessation of VPA reduced risk of foetal malformations to levels seen in the general population

Seizure control was worse when VPA was ceased or reduced

Introduction

The action of the European Medicines Agency to recommend significantly limiting the use of valproate (VPA) in those capable of becoming pregnant [1], and the possibility that other drug regulatory agencies providing similar advice, has raised concerns among neurologists because of fears for decreased control of epileptic seizure disorders where VPA is currently the most effective available agent [2]. No quantitative information is yet available from clinical practice concerning the magnitude of change that restricting VPA use will achieve regarding foetal malformation rates and seizure disorder control during pregnancy in the same population, though there is a recent publication demonstrating decreased control of genetic generalised epilepsy when VPA therapy was withdrawn in preparation for pregnancy in 28 cases [3].

The Raoul Wallenberg Australian Register of Antiepileptic Drugs in Pregnancy (APR) contains information about an appreciable number of women who were taking VPA for epileptic seizure control and in whom the drug was withdrawn, wholly or partly, in anticipation of pregnancy. This data is analysed to obtain insight into the effects of withdrawing VPA on the hazards of foetal malformation and maternal seizure control, compared to pregnancies where the existing pre-pregnancy VPA treatment continued unaltered.

Materials and Methods

The APR has collected data on the pregnancies of Australian women with epilepsy since 1999. Most of these women were taking antiepileptic drugs (AEDs), but a minority had epilepsy that was untreated, at least in the earlier half of pregnancy. More complete information regarding the APR and its recruitment policies and data handling practices has been published previously [4, 5]. In brief, Australian women with epilepsy, when pregnant or planning pregnancy could be enrolled voluntarily in the Register, which has been estimated to contain information on about 8.7% of the relevant pregnancies in Australia [6]. All contact between pregnant women and the APR is *via* telephone. Information concerning each woman's pre-pregnancy epilepsy and the course of her pregnancy is recorded (i) at enrolment, (ii) at approximately 28 weeks of pregnancy, (iii) within the first post-partum month and (iv) as far as possible, at one year after giving birth. Whenever possible, the accuracy of the information provided by pregnant women is confirmed by their treating medical practitioners, who retain control of the clinical management of the pregnancies throughout. Over the course of its existence, the APR has been under the oversight of various Melbourne based institutional ethics committees, that of Melbourne Health (The Royal Melbourne Hospital) currently holding responsibility. All participants provide written informed consent to be involved in the APR.

Foetal malformations recorded in the APR are structural, categorised according to the Victorian Birth Defect classification [7] and were recognised by the time of the post-natal interviews. Additional malformations were sometimes detected during the post-pregnancy year. These late recognised malformations, mainly quite minor ones, are not been considered in the present study, because of loss of contact with some women beyond the post-natal interviews.

It was not practicable for the women concerned to keep seizure diaries throughout their pregnancies, and they had not kept such records before becoming pregnant. Consequently, the accuracy of information recorded concerning seizure activity depended on the recall of the women involved. Seizure activity had to be analysed on a present or absent basis over particular time-based stages of the study, viz, pre-pregnancy, pregnancy, labour and post-natal, the information being provided by the women involved at the times of scheduled telephone interviews. Seizures occurring in the pre-pregnancy year were considered evidence of underlying 'active' epilepsy, while seizure freedom over that year constituted 'inactive' epilepsy in relation to pregnancy. The one-year cut-off was used because a previous analysis of the Register's data [8] had shown a clear difference in the chance of seizure-free pregnancy with longer periods than one year of pre-pregnancy seizure control, and because, in obtaining retrospective data, patients seemed to find it easier to recall their situations 12, as compared with 9, months before.

The APR in late 2019 contained information on 2233 pregnancies in women with epilepsy. Not considering further 25 pregnancies in which VPA dosage had been increased before pregnancy, there were 52 pregnancies in which the VPA dose had been reduced before pregnancy and a further 106 in which it had ceased altogether. In the present paper the outcomes in *these 158 pregnancies* are compared with those in the *remaining 422 pregnancies* in which VPA doses or the doses and natures of any other AED had not been changed before pregnancy. The pre-pregnancy changes in VPA therapy had occurred within 50 days of the last menstrual period in 5.3% of the pregnancies studied, within 100 days in 39.1% and within 200 days in 70.7%. The pregnancies where VPA dosage was unchanged had a mean gestational age of 21 weeks; the corresponding figure for those where changes in VPA therapy had been made was 19 weeks.

Relevant data from the APR were transferred to an Excel spreadsheet and then analysed, employing confidence interval statistical methods, a $P<.05$ value being considered as statistically significant. In calculating occurrence rates of various items studied, the denominators used were the numbers of instances for which the relevant information had been recorded.

Results

VPA use declined progressively with time as a proportion of total AED use in the study population, while the drug tended to be involved in an increasing proportion of pre-pregnancy treatment changes (upper panel - Figure 1). Until around 2010 the proportions of pregnancies involving VPA dosage reduction and cessation of intake tended to remain fairly constant. Thereafter, there appeared to be an increased tendency for cessation of VPA intake rather than dosage reduction to occur before pregnancy (lower panel – Figure 1). When was fully withdrawn, it was replaced by carbamazepine on 10 occasions, by clonazepam on five, by gabapentin on two, by levetiracetam on 23, by lamotrigine on 40, by phenytoin on one, and by topiramate also on one. Combinations of two replacement agents were employed on six occasion ns. No replacement AED was prescribed in 28 of the 106 pregnancies (26.4%) when VPA ended.

When VPA was replaced by lamotrigine, used in monotherapy before pregnancy, the rate of occurrence of seizure-affected pregnancies was 15 in 34 (44.1%), and the rate of convulsive seizure-affected pregnancies 6 in 34 (17.6%). With levetiracetam replacement in the same situation, the rates were, respectively, 9 in 21 (42.9%) and 6 in 21 (28.6%). In the 28 pregnancies where no antiepileptic drug had replaced VPA, by the 7th month of pregnancy AED therapy had been resumed in 10 (by VPA in 8), and by term in 14 (VPA in 11). Of the latter 14 pregnancies, seizures had recurred in 8, with convulsive seizures in 7 of the 10: of the 14 that remained untreated throughout pregnancy, seizures had occurred in only two pregnancies, and convulsive seizures in none.

The women involved sometimes provided observations regarding their changed therapy, but none seemed to explain her understanding of the medical thinking that underlay the changes.

Characteristics of the groups studied

Table 1 compares certain characteristics of the pregnancies in which VPA intake was ceased or the dose reduced before pregnancy and in the two subgroups within this category (viz. VPA dose-reduced and VPA intake ceased) with the corresponding data from the pregnancies in which VPA therapy was unaltered.

Referral to the APR by neurologists was more frequent in the pregnancies where VPA therapy was altered (59.5% versus 42.8%; O.R. = 1.592, 95% C.I 1.099, 2.307). The neurologist referral rates were reasonably similar in the two treatment-changed subgroups.

Generalised epilepsies were less common when VPA treatment was changed than when it was unaltered (65.6% versus 85.8%; O.R. = 0.460, 95% C.I. 0.304, 0.696). Within the treatment-changed sub-groups generalised epilepsy was little more frequent when VPA dose was decreased than when the drug was ceased.

Epilepsy was less often inactive before pregnancy in the treatment-changed group than the control group, 58.9% *v* 65.9%, but the difference was not statistically significant. Pre-pregnancy epilepsy inactivity rates were very similar in the two treatment-changed subgroups.

Mean VPA doses were higher before pregnancy in the treatment-changed group (1058 ± s.d. 632.6 mg per day) than in the treatment unchanged comparator group (887 ± s.d. 586.8 mg per day), the difference of 173.3 mg per day having a 95% confidence interval of 63.53 to 283.1 mg per day. Pre-pregnancy mean VPA doses had been higher in the subgroup in which the dosage was decreased than in the subgroup where the drug was ceased.

Foetal outcomes

At the time of the postnatal assessment, there was a foetal malformation rate of 10.9% in the pregnancies where VPA dosage was not changed, but a malformation rate of 4.5% where the treatment had been changed (hazard ratio = 0.412; 95% C.I. 0.190, 0.892). Within the treatment-changed subgroups, the malformation rate was 7.7% when the drug dosage had been reduced, but 2.9% when use of the drug had ceased before pregnancy (hazard ratio = 0.262; 95% C.I., 0.083 to 0.826). relative to pregnancies where VPA dose had been unchanged. The 2.9% malformation rate in the VPA untreated pregnancies was lower, but not statistically significantly so, than the 3.6% rate in comparable pregnancies in the whole APR database viz. those where therapy had not been changed before pregnancy and where there was no VPA intake (O.R. = 0.781; 95% C.I. 0.240, 2.547).

Seizure control

During pregnancy seizures occurred in 30.8% of the VPA treatment-unchanged group, but in 46.2% of the treatment-changed ones (Table 1; hazard ratio = 1.500, 95% C.I. 1.203, 1.870). For convulsive seizures the corresponding figures were 17.5% and 22.8% (hazard ratio = 1.299, 95% C.I. 0.952, 1.851). Seizure-affected pregnancy rates were relatively similar in the two subgroups within the treatment-changed category. Seizures had occurred in 45 of 101 pregnancies in women with genetic generalised epilepsies (44.6%), with convulsive seizures occurring in 24 (23.8%). The corresponding figures for 53 pregnancies with focal epilepsies were 24 (45.3%) and 10 (18.9%). Considering only pregnancies where all VPA intake had been ceased, for generalised epilepsies the corresponding figures were 27 in 64 (42.2%) for any seizures, and 18 in 64 (28.1%) for convulsive ones, and for focal epilepsies 17 in 38 (44.7%) and 6 in 38 (15.8%). No differences were statistically significant at the P<.05 level.

When epilepsy had been inactive in the pre-pregnancy year, seizure-affected pregnancy rates were a little higher in the treatment-changed group than in the treatment-unchanged group (17.2% *versus* 14.4%, O.R. = 1.236; 95% C.I. 0.656, 2.381). When the pre-pregnancy epilepsy had been active, the rates were statistically significantly higher in the treatment-changed group (87.7% *versus* 62.5% (hazard ratio = 1.408, 95% C.I. 1.200, 1.640). In the VPA dose-reduced and VPA-ceased subgroups, seizure-affected pregnancy rates were reasonably similar when the pre-pregnancy epilepsy had been inactive (20.0% and 15.9% respectively), and when it had been active, though much higher in the latter situation (86.4% and 88.4% respectively).

VPA intake had been resumed by 7 months of pregnancy in 9 of the 106 pregnancies where the drug had been withdrawn, and in 15 by the time of giving birth. Consequently, the above seizure-affected pregnancy rates may provide underestimates of what the situation might have been in complete absence of resumed VPA intake.

Intra-partum and post-partum seizure rates were reasonably similar in both the groups and subgroups studied.

Rates of seizure-affected pregnancy were reasonably similar after VPA withdrawal or dosage reduction in 45 of 101 pregnancies in women with genetic generalised epilepsies (44.6%) or in 52 (50.5%) if intra-partum and immediate post-partum seizures were included. The corresponding numbers in 53 pregnancies in women with focal epilepsies were 24 (45.3%)

or 29 (54.7%). Within the generalised epilepsy category the hazard of seizures during 61 pregnancies where the pre-pregnancy year had been seizure-free was 19.7% (12/61), or 31.1% (19/61) if intra- and post-partum seizures were included, but substantially higher if seizures had occurred in the pre-pregnancy year (33/40 = 82.5%).

Pregnancies affected by convulsive seizures were also more frequent, though not statistically significantly so, in the VPA dose-decreased or ceased group, that in the VPA dose unchanged group (46.2% versus 30.8%, Relative risk 1.299, 95% C.I. 0.912, 1.851, and in the drug withdrawn group (45.3% versus 30.8%, Relative risk 1.399, 95% C.I. 0.914, 2.072).

In all, withdrawing VPA before pregnancy appeared to have substantially decreased the hazard of foetal malformation (by up to 75%), but at the cost of a 50% increase in the hazard of losing seizure control during pregnancy.

Discussion

The APR data and its analysis have several limitations. The Register does not necessarily involve a random sample of pregnant Australian women with epilepsy, but merely those who volunteered to enrol. A condition of enrolment was that each woman's own medical attendants control the pregnancy management and clinical decision making, so that what this paper's authors might consider optimal treatment, e.g. management guided by AED concentration management, full compliance with prescribed therapy, cannot necessarily be assumed to have occurred. In essence, this paper reports what happened to a cohort of pregnant women with epilepsy managed by others rather than by the paper's authors and does not describes a planned study involving a matched control design. Because of these and other limitations, extrapolation from its findings to the situation in the wider community of pregnant women with epilepsy should be made with due caution. However, it reports data not to our knowledge available elsewhere in the literature.

Why was VPA therapy altered before pregnancy in some 27% of the pregnancies studied, and not in all? No direct testimony from those who presumably instigated the changes is available, but data in the APR, and general awareness of the Australian situation at the relevant times, provide clues. The possible reasons for changing treatment would be to

achieve better seizure control, to relieve drug adverse effects and to decrease foetal exposure to a possible teratogen, purposes that are not mutually exclusive.

The majority of the pregnancies studied occurred in women with generalised epilepsies, for which VPA is generally accepted to be the most effective available agent. It seems unlikely that doses of this drug would be reduced, or its intake ceased, to improve seizure control in this type of epilepsy. In the minority of pregnancies where the epilepsy was focal, and where there are several available effective alternatives to VPA, that drug may have been withdrawn to make way for another appropriate agent to improve seizure control. Nevertheless, in 28 pregnancies VPA was withdrawn and not replaced.

There were no reports of withdrawal of VPA to relieve unwanted effects in the APR database, and it seems unlikely that many women would have been allowed to experience unwanted effects when such a high proportion of them had contact with neurologists.

Reducing the hazard of foetal malformation therefore seems likely to have been a frequent motive underlying the VPA withdrawal before pregnancy. However, the teratogenicity of the drug was not widely appreciated in the earlier part of the first decade of the 21st Century, though it was not unknown [9]. Then for a time it was thought that there was a safe VPA dose from the teratogenicity standpoint [10], before it became increasingly recognised that the foetal malformation hazard increases progressively with maternal drug dose [11, 12]. The time-related data of Figure 1 tend to correlate with increasing awareness of VPA-related teratogenicity, and with the increasing replacement of VPA dose reduction by cessation of all intake of the drug as reasonably satisfactory low teratogenicity alternatives to the drug for the management of generalised epilepsies became available, viz. lamotrigine and levetiracetam, though neither of these agents is regarded as first line by the Australian Government for use in genetic generalised epilepsies, although extensively employed by Neurologists .

The types of outcome of the altered VPA treatment policy were as might have been expected from earlier data, viz, fewer foetal malformations but loss of seizure control during pregnancy in some women. The magnitude of these changes is an important consideration.

Ceasing all VPA intake yielded a foetal malformation rate of just below 3%, a value which is sometimes taken as the malformation rate which applies in the general pregnant

population. The price paid for this gain was a 50% increase in the hazard of seizure affected pregnancy with, despite the frequent involvement of neurologists in the situation, a 40% increase in the likelihood of seizure-affected pregnancy if epilepsy before pregnancy was already active. The APR does not contain information regarding the various difficulties and other problems that may arise from the loss of previous freedom from seizures, but one matter needs mention. Under contemporary Australian conditions, seizure freedom for a year or longer roughly equates with the right to drive a motor vehicle for private purposes. Loss of this ability because of return of seizure disorder activity constitutes a major source of disruption of domestic and social life for mothers, and their family. From the present material, the car driving issue should have affected mainly women with inactive pre-pregnancy epilepsies, where the risk of loss of seizure control was initially less than in women with active pre-pregnancy epilepsy.

The extent to which this experience of the consequences of withdrawing VPA or reducing its dosage prior to pregnancy can be applied more widely to women with epilepsy who are capable of pregnancy, and to their seizure control irrespective of pregnancy, remains uncertain till further information becomes available. It is difficult to relate the present findings to the recently published experience of Cerelli Irelli et al [3], who studied genetic generalised epilepsy in 28 women in whom VPA was withdrawn for the purpose of pregnancy. In these women it was stated that their epilepsy became clinically worse. It was unclear whether they had actually become pregnant, and also whether seizures occurred during pregnancy. These authors worked to a criterion of seizure freedom for at least 18 months. The recent large-scale study of Tomson et al [13], describing the consequences of changing patterns of AED use, which included decreased VPA use, in pregnant women with epilepsy between 2000 and 2013, found a decreased hazard of foetal malformation without appreciable deterioration in generalised tonic-clonic seizure control. The present study obtained a similar finding in relation to teratogenicity. However, tonic-clonic seizure control appeared worse, though not statistically significantly so.

It seems likely that, if Australian women with epilepsy, who would have previously been managed with VPA undertake pregnancy and have ceased taking the drug, their risk of having a malformed foetus will not greatly differ from that which applies to women in general. While the APR can provide no information on cognition, it seems not unreasonable

to expect that the hazard of their infants experiencing neurodevelopmental delays [14] will also be lessened. In contrast to these substantial benefits, the experience of the present investigation suggests that appreciable numbers of women with genetic generalised and other epilepsies will be disadvantaged by impaired control of their seizure disorders. The possible advent of new AEDs that are effective in managing genetic generalised epilepsies will not quickly alleviate the situation because, as happened with VPA, many years may have to pass before sufficient information can be obtained to assure human foetal safety. Until then, a continuing situation regarding VPA is likely to exist that will require some subtlety of clinical judgement. An imposed restriction of possible courses of action and attendant possible legal implications add a degree of inflexibility that may not always prove advantageous.

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Conflicts of Interest

F J E Vajda has received research support for the Australian Pregnancy Register from the Epilepsy Society of Australia, NHMRC, RMH Neuroscience Foundation, Epilepsy Action, Sanofi-Aventis, UCB Pharma, Janssen-Cilag, Novartis, and Sci-Gen.

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J E Graham, AA Hitchcock, C M Lander and M J Eadie have no relevant conflicts of interest to declare.

Ethical Publication Statement

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

Table 1. Characteristics of the women involved in the pregnancies studied, and details of the pregnancy outcomes and seizure disorder control. VPA doses are in mg/day (mean ± s.d.).

	VPA unchanged N=422		**VPA changed N=158**		**VPA dose reduced N=52**		**VPA ceased N=106**	
Before pregnancy								
Age (years)	30.4 ± 5.2		31.0 ± 4.2		31.9 ± 3.7		30.6 ± 4.4	
Previous VPA dose	884.7 ± 586.8		1058 ± 626.6		1161 ± 582.8		996.3 ± 646.7	
Changed VPA dose	884.7 ± 586.8		234.8 ± 392.4		629.6 ± 409.6		0	
	Rate	**%**	**Rate**	**%**	**Rate**	**%**	**Rate**	**%**
Neurologist referral	202/421	48.0	94/158	59.5	29/52	55.8	65/106	61.3
Primipara	180/421	42.8	89/158	56.3	30/52	57.7	59/106	55.7
Generalised epilepsy	323/401	80.5	101/154	65.6	37/52	71.2	64/102	62.7
Focal epilepsy	78/401	19.5	53/154	34.4	15/52	28.8	38/102	37.3
Inactive epilepsy	278/422	65.9	93/158	58.9	30/52	57.7	63/106	59.4
Taking no AEDs	0/422	0	28/158	17.7	0/52	0	28/106	26.4
AED monotherapy	240/422	56.9	131/158	82.9	34/52	65.4	69/78 [#]	87.2
Outcomes – foetal								
Live born normal	362/422	85.8	146/158	92.4	46/52	88.5	100/106	94.3
Abortions	12/422	2.8	2/158	1.3	1/52	1.9	1/105	0.95

Stillbirths	1/422	0.24	2/158	1.27	1/52	1.0	1/106	0.94
Malformed foetuses	46/422	10.9	7/156	4.5	4/52	7.7	3/105	2.8
Outcomes – seizures								
Seizures in pregnancy	130/422	30.8	73/158	46.2	25/52	48.1	48/106	45.3
Convulsive seizures in preg.	74/422	17.5	36/158	22.8	10/52	19.2%	26/106	24.5%
Seizures in labour	5/397	1.3	6/151	4.0	0/49	0	6/102	5.9
Seizures in post-natal weeks	88/397	22.2	36/151	23.8	13/49	26.5	23/102	22.5

[#] those taking AEDs after treatment change

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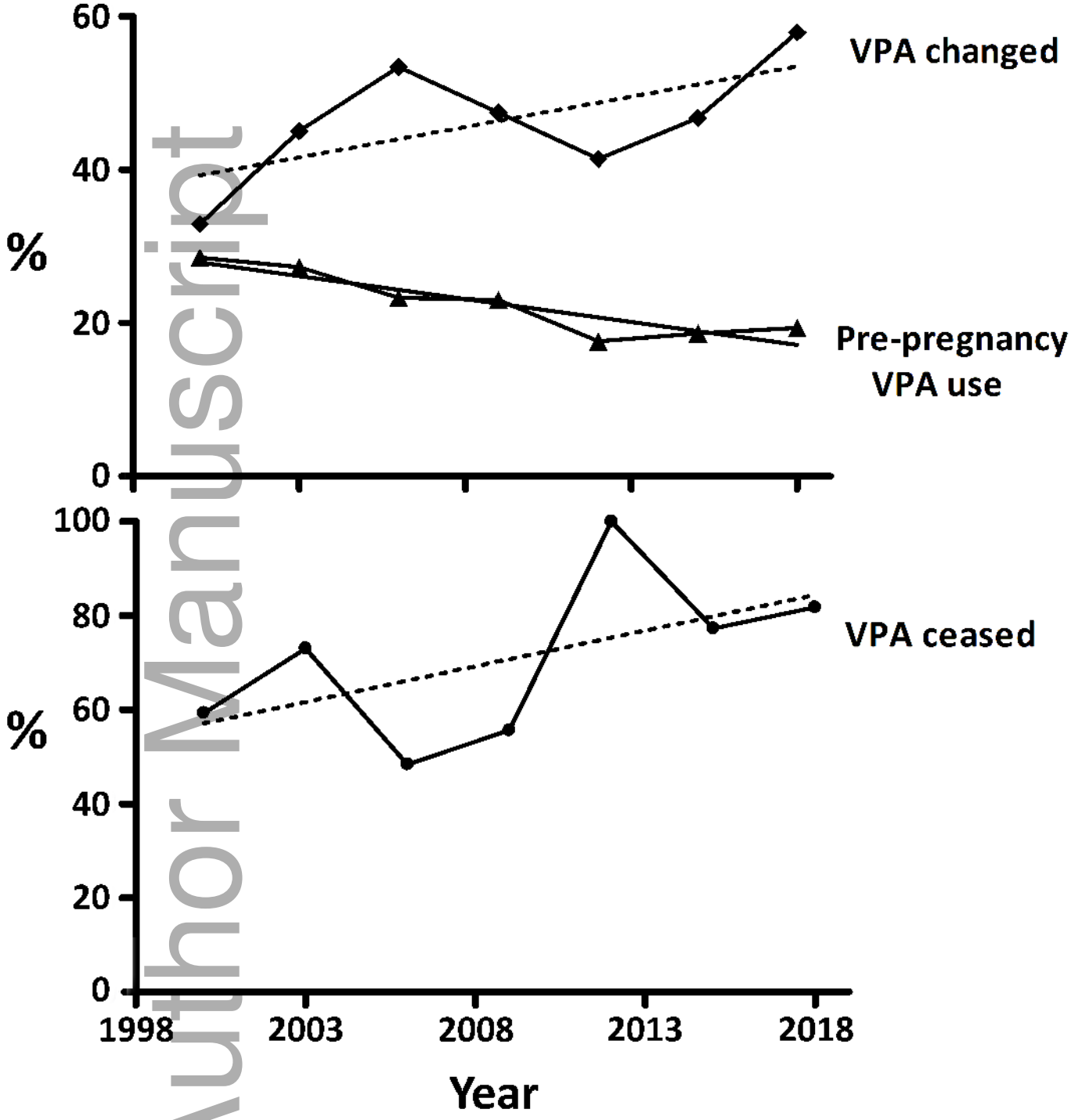
Figure Legend

Figure 1: Top panel. Declining proportion of all APR pregnancies over two decades where VPA was used before conception in women with epilepsy [Regression, % = 1228 – 0.6000 year; P=0.0041] and trend to increasing proportion of pregnancies where the change in treatment made involved VPA [Regression, % = 1542 + 0.7905 year; P = 0.1260].

Lower panel. Trends to increasing cessation of VPA therapy with time rather than VPA dosage reduction, when VPA therapy was altered before pregnancy [% = -2983 + 1.520 year, P = 0.1952].



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