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Specific fetal malformations following intrauterine exposure to antiseizure medication

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ABSTRACT

Objective: To investigate in the Australian Pregnancy Register of Antiepileptic Drugs patterns of fetal malformation associated with intrauterine exposure to particular currently available antiseizure medications taken by women with epilepsy.
Results: There was statistically significant evidence ($P < 0.05$) of an increased hazard of fetal malformation associated with exposure to valproate, carbamazepine, topiramate, zonisamide, and with conception after assisted fertilization, but a reduced hazard in the offspring of women who continued to smoke during pregnancy. Valproate exposure was associated with malformations in a wide range of organs and organ systems, carbamazepine and topiramate with hydronephrosis, topiramate also with hypospadias, zonisamide with spina bifida and assisted fertilization with heart and great vessel maldevelopment.
Conclusions: Prenatal valproate exposure appears to interfere with the development of many if not all, fetal tissues. It seems likely that prenatal exposure to carbamazepine and topiramate, and possibly exposure to zonisamide, but also some process related to in vitro fertilization, may more selectively affect the normal development of particular fetal tissues or organs.

1. Introduction

A decade ago, we investigated the relationship between prenatal exposure to particular antiseizure medications (ASMs) and specific types of fetal malformation in the data recorded in the Raoul Wallenberg Australian Pregnancy Register of Antiepileptic Drugs (APR) [1]. At that time material from 1703 pregnancies was available, and in the interval, relevant data from more than 700 additional pregnancies accumulated. With this enlarged database and the availability of newer ASMs and changes in the pattern of usage of these agents, it seemed worth re-investigating the matter to see if new insights could be obtained into the patterns of malformation associated with individual ASMs.

The results of this investigation are described below.

2. Materials and methods

2.1. The APR

The APR has been in existence since 1999, accumulating data concerning the pregnancies of Australian women with epilepsy (WWE) who have voluntarily enrolled their pregnancies in the Register's database either before or during their current pregnancy after becoming aware of the APR's existence. More extensive details of the Register's activities, including its recruitment policies and practices, have been published previously [2]. The WWE whose details are included in the Register had been taking ASMs prior to, and throughout pregnancy, or were not treated with these drugs, at least in the earlier months of pregnancy. Over its 22-year existence, the APR is thought to have accumulated data on about 8.7% of the relevant pregnancies that are estimated to have occurred in Australia [3].

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All contact between pregnant women and the Melbourne-based APR has been by telephone. The APR contains data concerning each woman's medical details, pre-pregnancy epilepsy situation and the course of her pregnancy recorded (i) at her time of enrolment, (ii) at approximately 28 weeks of pregnancy, (iii) around the end of the first post-partum month and, whenever possible, at (iv) a year after the end of the pregnancy. As far as feasible, the accuracy of the information provided by the pregnant women has been confirmed by their treating medical practitioners, in whose hands the clinical management of the women has always remained, uninfluenced by the APR's personnel. Over the years of its existence, the APR has been continuously under the oversight of various Melbourne-based institutional Human Research Ethics Committees (HRECs), with the HREC of Melbourne Health, currently being responsible. All women enrolled have provided written informed consent for their data to be recorded and utilized.

2.2. Data analysis

After extraction of relevant items of information into a spreadsheet, APR data have been analyzed by conventional statistical techniques, mainly logistic regression using the statistics package Stats Direct, taking a $P < 0.05$ level of confidence as being statistically significant.

The roles of the following potentially relevant factors for which information had been recorded in the APR database were investigated in relation to the occurrence of fetal malformation overall and to that of specific malformations. This was done by fitting multivariate logistic regressions, followed by repeated serial stripping of unlikely candidate covariates until a regression emerged with statistically significant or nearly statistically significant parameters (without adjustment for possible consequences of multiple comparisons). The initial co-variates studied were: daily dosages of carbamazepine (CBZ), valproate (VPA), lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM), phenytoin, clonazepam, oxcarbazepine, gabapentin, perampanel, lacosamide, phenobarbitone, zonisamide (ZON); the number of ASMs used, maternal age, family history of fetal malformation, year of pregnancy, use of artificial fertilization, maternal parity, number of previous stillbirths, previous fetal malformation, folate intake before and during pregnancy, smoking during pregnancy, drinking alcohol during pregnancy, using marijuana, bearing twins, experiencing seizures in early pregnancy.

3. Results

3.1. Malformations overall

A total of 2479 pregnancies with known fetal outcomes, at least to the end of the first post-partum month, were available for analysis. Of these, 201 pregnancies had not involved the intake of ASMs during the earlier months of pregnancy, the stage when fetal maldevelopment was likely to have been initiated. These 201 pregnancies resulted in 7 offspring being born with fetal malformations (3.48%). Of the remaining 2278 pregnancies with ASM intake throughout pregnancy, 152 produced offspring with fetal malformations (6.67%: Odds Ratio = 1.9518; 95% C.I. = 0.9158, 4.2871). For the 1634 pregnancies where only a single ASM was involved throughout, the fetal malformation occurrence rate was 6.39%; for the 644 pregnancies involving ASM polytherapy, the corresponding rate was 7.61% (Odds Ratio = 1.2241; 95% C.I. = 0.8600, 1.7424).

The statistically significant logistic regression equation for the overall proportion of pregnancies involving fetal malformation that resulted after serial deletion of unlikely co-variates for the relationship was:

Logit of Malformation rate = −2.988669 + 0.000819 CBZ dose + 0.001484 VPA dose − 0.001645 LTG dose + 0.002588 TPM dose + 0.963892 proportion after assisted fertilization − 0.038687 proportion who smoked in pregnancy.

The individual covariate P values in the equation were: CBZ 0.0058, VPA < 0.00001, LTG 0.0769, TPM 0.0302, assisted fertilization 0.0068, smoking 0.0392. It is noteworthy that LTG dosage and smoking during pregnancy probably appeared associated with reduced calculated fetal malformation hazards.

The numbers of the individual ASMs and other co-variates incorporated in the above equation, and in some of the following data were: CBZ, 656 pregnancies; VPA 531; LTG 805; LEV 455; TPM 174; ZON 14, and assisted fertilization 169, family history of malformation 383, alcohol intake in pregnancy 364 and tobacco smoking 231.

3.2. Specific malformations

The individual statistically significant regression co-variates for the hazard of the occurrence of those specific fetal malformations for which there were at least 8 instances in the APR database, with indications as to their corresponding P values, are shown in Table 1. The actual statistically significant logistic regression equations are shown in Table 2.

Assisted fertilization measures had been employed in 168 of the pregnancies. *In vitro* fertilization had occurred in 95 pregnancies of these, hormonal measures only had been employed in 50 pregnancies, artificial insemination in 12, and there were no details of the measures employed recorded in 11 pregnancies. The associated fetal malformation rates were 9.47% in the *in vitro* fertilization pregnancies, and 14% in the hormonally-assisted ones, both rates higher than the overall 6.47% rate for the whole case series. As well, 8 of the 9 malformations that occurred in the *in vitro* fertilization pregnancies involved the heart and/or the great vessels, whereas 4 of the 7 malformations in the hormonally facilitated pregnancies involved the same structures.

4. Discussion

The findings of the present study are largely consonant with those obtained in the analysis of the smaller case series that was available a decade ago. However, in the current enlarged dataset, there is evidence of the occurrence of malformations involving additional body systems and structures in association with *in-utero* VPA exposure, viz. malformations of the mouth and local facial structures and hypospadias. Thus, VPA seems capable of interfering with the pre-natal development of most, though perhaps not of all, body tissues, since there were no statistically significant incidences of hydronephrosis and skull suture abnormalities recorded in relation to the drug, whereas the other associations were, in general, highly statistically significant (several with a p-value of <0.0001). However, hydronephrosis has been reported associated with VPA exposure in another study [4] and craniosynostosis in the study of Jentink et al [5]. CBZ exposure has continued to be associated with hydronephrosis, but not with other malformations, while malformations associated with TPM exposure seem to be largely confined to the genital-urinary organs. Although it had only a very small usage in the APR data, the findings suggested that ZON may have some potential for teratogenicity. This was also the case for the McCluskey et al study [6] though neither investigation yielded conclusive data. In this connection, it is interesting to note that both it and topiramate are carbonic anhydrase inhibitors.

Table 1
Statistically significant hazards of specific fetal malformations associated with intrauterine exposure to individual ASMs, assisted fertilization, maternal tobacco smoking, and year of pregnancy. Asterisks are used in the conventional way to indicate P values (*=<0.05; ** <0.01; *** <0.001. **** <0.0001). Items within brackets have P values in the range <0.10 to 0.05. Items tending to reduce calculated malformation risks are shown as being '-ve'.

Malformation	CBZ	LTG	LEV	TPM	VPA	ZON	Assisted Fertilis[n]	Smoking	Year
Overall	**	(-ve)		*	****		**	**-ve** *	
ASD/VSD					****	(+ve)	****		
PFO					***				**-ve** *
Great vessels					****		***		
Spina bifida					****	*			
Skull sutures								(+ve)	**-ve** **
Head clefts					***				
Hydronephrosis	**			*					
Hypospadias				***	****			(-ve)	
Undesc[d]. testes					**				**
Talipes					***				
Digits					****				

Table 2
Logistic regression results (P < 0.10) for hazards of specific fetal malformations.

Malformation	Logit of proportion with malformation
ASD/VSD	−4.947247 + 0.000837 VPA + 0.005598 ZON + 1.77641 assist fertilisation
P=	0.0002 0.069 < 0.0001
PFO	449.803725 + 0.000744 VPA − 0.227327 year
P=	0.0175 0.0285
Great vessels	−6.208909 + 0.001211 VPA + 2.142572 assist fertilisation
P=	<0.0001 0.0008
Spina bifida	−6.572502 + 0.001895 VPA + 0.008179 ZON
P=	<0.0001 0.0346
Skull sutures	581.875442−0.268262 Year + 1.312971 smoked
P=	0.0115 0.0660
Head clefts	−5.917269 + 0.000691 VPA
P=	0.0086
Hydronephrosis	−7.280386 + 0.001847 CBZ + 0.00457TPM
P=	0.0019 0.0389
Hypospadias	−4.920007 + 0.0011161 VPA + 0.00517 TPM − 1.853476 smoked
P=	<0.0001 0.0008 0.0953
Undesc[d]. testes	−10.605472 + 0.001321 VPA + 0.201175 year
P=	0.0043 0.0027
Talipes	−5.721799 + 0.000904 VPA
P=	0.0034
Digits	−5.776022 + 0.00096 VPA + 1.655121 FH malformations
P=	<0.0001 0.0006

An increased hazard of fetal malformation in pregnancies where conception was facilitated by assisted fertilization methods has been recorded in the literature previously (e.g. 7,8,9), and the present experience suggests that it also applies as a factor in its own right even if the women involved are taking ASMs, some of which may affect exogenous and endogenous hormonal biotransformation. The extent of the material that forms the basis of the present paper is too small to warrant more definite interpretations, though it does raise the possibility that procedures involved in vitro fertilization may have somehow contributed to maldevelopment in the heart and great vessels of the fetus.

The association found between tobacco smoking during pregnancy and a lowered overall and hypospadias malformation occurrence rate, yet a heightened rate of occurrence of skull suture synostosis, may appear surprising when there is a considerable amount of publication in the literature showing an increased fetal malformation rate in the offspring of women who smoked during pregnancy [10,11,12]. However, the recent analysis of Kjersgaard et al [13] provided good quality evidence in the sons of Danish women who smoked during pregnancy that supports earlier suggestions that there is a decreased risk of hypospadias associated with maternal smoking.

The association found in the present study between the year in which the pregnancy occurred and increased or decreased risks of certain fetal malformations suggests that there probably are other time-dependent factors involved in the situation explored in this paper, but ones that have not been identified in the study.

All of the malformation rates quoted above in relation to intrauterine ASM exposure necessarily contain a component that is not related to the drugs and which, in the present series, probably has a value of 3.48%, a figure not dissimilar to the widely accepted 3% malformation rate that applies for pregnancy in general. The figure also correlates with the 2.79% rate calculated from the overall logistic regression rate shown above when all individual ASM dosage values are set to zero.

Although the present paper is based on a reasonably sized population of women with epilepsy, the events that were studied are uncommon or rare within that population. The small numbers involved mean that the findings may sometimes be better regarded as pointing in certain directions rather than establishing them beyond doubt at the conventional P < 0.05 level of statistical significance. Further, the P values cited are not adjusted for possible consequences of multiple comparisons, because of uncertainty regarding the optimal method to employ. Readers will, no doubt, take into consideration the magnitude of individual P values in assessing the importance of the associated individual findings. Nevertheless, in the APR data there already seems to be reasonably persuasive evidence of non-specific organ teratogenicity in relation to prenatal VPA exposure, and a sufficient indication of possible more organ-specific teratogenicity in relation to at least CBZ, TPM, and ZON. These findings indicate the need for continuing investigation of the matter of medication-related teratogenesis in relation to currently available and likely forthcoming ASMs, and preferably investigations carried out in larger series of pregnancies if these can be obtained.

5. Conclusions

Based on the APR data, it appears very probable that in-utero VPA exposure may interfere with the development of many if not all, fetal tissues. It seems likely that prenatal exposure to CBZ and TPM, and possibly exposure to zonisamide, as well as some process related to *in vitro* fertilization, may more selectively affect the normal development of particular fetal tissues or organs. This

knowledge may provide one factor, among others, in determining the choice of antiseizure therapy in women with epilepsy.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FJE Vajda has received research support for the Australian Pregnancy Register from the Epilepsy Society of Australia, the Australian NHMRC, the RMH Neuroscience Foundation, Epilepsy Action Australia, Sanofi-Aventis, Eisai, UCB Pharma, and Sci-Gen. T O'Brien has received research support from the Epilepsy Society of Australia, the NHMRC, the RMH Neuroscience Foundation, Sanofi-Aventis, UCB Pharma, and Sci-Gen and Eisai. P Perucca is supported by an Emerging Leadership 2 Investigator Grant from the NHMRC (APP2017651), the Epilepsy Foundation, the Royal Australasian College of Physicians, The University of Melbourne, Monash University, the Weary Dunlop Medical Research Foundation, Brain Australia, and the Norman Beischer Medical Research Foundation. He has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma, outside the submitted work. He is an Associate Editor for Epilepsia Open. JE Graham, AA Hitchcock, CM Lander, and MJ Eadie have no relevant conflicts of interest to declare.

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References

[1] Vajda FJ, O'Brien TJ, Graham J, Lander CM, Eadie MJ. Associations between particular types of fetal malformation and antiepileptic drug exposure in utero. Acta Neurol Scand 2013;128(4):228–34. https://doi.org/10.1111/ane.12115. Epub 2013 Mar 6. PMID: 23461556.

[2] Vajda FJ, O'Brien T, Hitchcock A, Graham J, Lander C, Eadie M. The Australian antiepileptic drug in pregnancy register: aspects of data collection and analysis. J Clin Neurosci 2007;14(10):936–42. https://doi.org/10.1016/j.jocn.2006.08.015. Epub 2007 Jun 27. PMID: 17588763.

[3] Vajda FJ. The Australian Pregnancy Register of Anti-epileptic Drugs: 10 years of progress. J Clin Neurosci 2010;17(12):1485–8. https://doi.org/10.1016/j.jocn.2010.05.008. Epub 2010 Sep 9. PMID: 20829048.

[4] Huot C, Gauthier M, Lebel M, Larbrisseau A. Congenital malformations associated with maternal use of valproic acid. Can J Neurol Sci 1987;14(3):290–3. https://doi.org/10.1017/s0317167100026639. PMID: 3117346.

[5] Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al.; EUROCAT Antiepileptic Study Working Group. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 2010;362(23):2185–93. doi: 10.1056/NEJMoa0907328. PMID: 20558369.

[6] McCluskey G, Kinney MO, Russell A, Smithson WH, Parsons L, Morrison PJ, et al. Zonisamide safety in pregnancy: Data from the UK and Ireland epilepsy and pregnancy register. Seizure 2021;91:311–5. https://doi.org/10.1016/j.seizure.2021.07.002. Epub 2021 Jul 9. PMID: 34273670.

[7] Giorgione V, Parazzini F, Fesslova V, Cipriani S, Candiani M, Inversetti A, et al. Congenital heart defects in IVF/ICSI pregnancy: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2018;51(1):33–42. https://doi.org/10.1002/uog.18932. PMID: 29164811.

[8] Simpson JL. Birth defects and assisted reproductive technologies. Semin Fetal Neonatal Med 2014;19(3):177–82. https://doi.org/10.1016/j.siny.2014.01.001. Epub 2014 Feb 20. PMID: 24559658.

[9] Chung EH, Harris BS, Muasher SJ, Kuller JA. The risk of congenital anomalies by fertility treatment modality. Obstet Gynecol Surv 2021;76(1):37–47. https://doi.org/10.1097/OGX.0000000000000855. PMID: 3350687.

[10] Perry MF, Mulcahy H, DeFranco EA. Influence of periconception smoking behavior on birth defect risk. Am J Obstet Gynecol 2019;220(6):588.e1–7. https://doi.org/10.1016/j.ajog.2019.02.029. Epub 2019 Feb 18. PMID: 30790570.

[11] Bolin EH, Gokun Y, Romitti PA, Tinker SC, Summers AD, Roberson PK, et al.; National Birth Defects Prevention Study. Maternal smoking and congenital heart defects, National Birth Defects Prevention Study, 1997–2011. J Pediatr 2022;240:79–86.e1. doi: 10.1016/j.jpeds.2021.09.005. Epub 2021 Sep 8. PMID: 34508749; PMCID: PMC8712361.

[12] Deng C, Pu J, Deng Y, Xie L, Yu L, Liu L, et al. Association between maternal smoke exposure and congenital heart defects from a case-control study in China. Sci Rep 2022;12(1):14973. https://doi.org/10.1038/s41598-022-18909-y. PMID: 36056058; PMCID: PMC9440088.

[13] Kjersgaard CL, Arendt LH, Ernst A, Søndergaard Lindhard M, Olsen J, Henriksen TB, et al. Lifestyle in pregnancy and hypospadias in sons: a study of 85,923 mother-son pairs from two Danish pregnancy cohorts. Clin Epidemiol 2022;14:149–57. https://doi.org/10.2147/CLEP.S335877. PMID: 35173488; PMCID: PMC8841293.