Published in final edited form as:

Nat Rev Neurol. 2014 November ; 10(11): 614–616. doi:10.1038/nrneurol.2014.179.

Pregnancy in women with epilepsy—risks and management

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Abstract

The risks of seizures and antiepileptic drug (AED) teratogenicity must be balanced when treating pregnant women with epilepsy. Two recent articles address these risks for newer AEDs. Lamotrigine and levetiracetam carried low risks of malformations, and topiramate exhibited a dose-dependent risk. Levetiracetam controlled seizures more effectively than lamotrigine and topiramate.

Although the majority of children born to women with epilepsy are healthy, both mother and child are at increased risk of poor pregnancy outcomes. Antiepileptic drugs (AEDs) are among the most common teratogenic drugs prescribed to women of childbearing age, posing possible risks of congenital malformations and neuropsychological impairments. AED teratogenicity should be considered during drug selection for all women of childbearing potential, as many pregnancies are not planned, and most women with epilepsy cannot stop AED treatment due to the danger that seizures present to both mother and fetus. Balancing these risks to ensure the best pregnancy outcomes is challenging, and made more difficult by gaps in the evidence base that we need to direct care appropriately. Differential risks are known for some AEDs, and since 2000 our knowledge has increased markedly, but numerous unanswered questions remain. The specific risks associated with many AEDs are uncertain, due in part to the introduction of multiple new AEDs in the past two decades. Recently, investigators from the Australian Pregnancy Registry (APR) have published two articles that confirm prior findings and offer new insights.^{1,2}

In one of these articles, Vadja *et al.* provide an update on teratogenicity of AEDs introduced since 1990.¹ They reported that in 1,725 pregnancies, rates of fetal malformations associated with monotherapeutic exposure to lamotrigine (4.6%), levetiracetam (2.4%) and topiramate (2.4%) were not significantly higher than the malformation rates in children born to women with epilepsy who were not exposed to AEDs during the first trimester (3.3%). By contrast, the malformation rate associated with the older AED valproate (13.8%) was higher than the rate in the unexposed group. The only other older AED included in this study, and that was used by a large sample group, was carbamazepine, which was associated with a malformation rate (5.5%) that did not differ significantly from that of the unexposed group.

“...the factors that contribute to an increased risk of seizures during pregnancy ... are unclear“

Teratogens are expected to act in a dose-dependent manner. Vajda *et al.* found that valproate exhibited a dose-dependent effect, as seen in many previous studies.^{3,4} However, the only other AED that exhibited a dose-dependent effect was topiramate, for which such an effect has not been previously reported. In addition, topiramate was associated with a higher malformation rate when used in polytherapy (14.1%) than when used as monotherapy.

This report from the APR has similar limitations to other pregnancy registries: although these registries are prospective, AED treatment is not randomized, and sample sizes for some AEDs are limited. Consequently, we need to examine multiple studies to estimate the malformation rates for specific AEDs, so it is important that findings are reproducible across registries even though methodologies vary. In the APR, the lower overall rates of malformations with levetiracetam and lamotrigine are consistent with prior studies,^{3–5} even though the sample size for the levetiracetam group was relatively small. The overall rate of malformations associated with topiramate as monotherapy was lower in the APR than in other studies (4.2–4.9%),^{4,6,7} but the higher rate of malformations when topiramate was used in polytherapy raises concerns of interactive effects. Few data are currently available on the risks of specific polytherapy combinations, except for those including valproate. Some previous studies have found an increased incidence of cleft lip and/or palate in children born to women treated with topiramate during pregnancy.^{4,6–8} The present study did not replicate this finding, but did find an increased incidence of hypospadias, which has been noted once before in association with this drug.⁶

Dose-dependent effects of AEDs may not be apparent if sample sizes are inadequate, and small sample sizes may explain why such effects were not seen for most AEDs that were included in the APR study. The European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP), which includes the APR, is the largest AED pregnancy registry, and has reported dose-related teratogenic effects for all four of the AEDs with the largest sample sizes in its study: carbamazepine, lamotrigine, phenobarbital and valproate.³ Overall, the highest malformation rates were seen for valproate and the lowest for lamotrigine.

The second recent publication by the APR examined the effectiveness of the newer AEDs in controlling seizures during 1,534 pregnancies.² The most commonly used AEDs, in order of frequency, were carbamazepine, lamotrigine, valproate, levetiracetam, topiramate and phenytoin. Overall, seizures during pregnancy were more common with the newer AEDs (48.3%) than with older AEDs (34.8%) when used in monotherapy (OR 1.75). This difference was still present when the analysis was limited to the most dangerous seizures (that is, convulsions), regardless of whether they were due to focal or generalized epilepsy. From 2008–2013, convulsions occurred in 23.7% of patients taking newer AEDs and 14.2% who were taking older AEDs (OR 1.87). However, rates of all seizures in pregnant women taking levetiracetam were comparable to those for older AEDs (OR 0.87), and were significantly lower than for lamotrigine (OR 0.44) and topiramate (OR 0.38).

Although pre-pregnancy seizure frequency is predictive in part, the factors that contribute to an increased risk of seizures during pregnancy in women with epilepsy are unclear. An increased risk of seizures in pregnant women treated with lamotrigine and oxcarbazepine has been reported,^{9,10} but this risk has not previously been noted with topiramate use. The lower

risk of seizures with levetiracetam treatment during pregnancy demonstrated in the second APR study² has not been reported before; in fact, in a small study that included only 15 women who used levetiracetam monotherapy, 47% of the participants experienced an increase in seizure frequency during pregnancy.⁹ The increase in seizure frequency seen with lamotrigine use in the APR study may be partly attributable to increased clearance of the drug during pregnancy, and may be mitigated to some extent by dosage adjustment to correct for reduced blood levels. However, similar clearance changes are also seen with levetiracetam,⁹ but in the present study at least, this clearance did not have the same effect on seizures as it did in the case of lamotrigine.

Vadja *et al.* note that the combination of low teratogenic abnormalities and good seizure control during pregnancy make levetiracetam a good choice for women with childbearing potential.² A similar conclusion could be reached for carbamazepine. Lamotrigine is associated with low teratogenic risks, but higher risks of seizures; however, monitoring of blood levels and adjusting the dosage during pregnancy may reduce the seizure risk. Oxcarbazepine has a similar profile to lamotrigine, although we lack cognitive outcome data for this drug. Topiramate seems to carry an intermediate teratogenic risk, while valproate clearly poses the greatest teratogenic risk, followed by phenobarbital.

The two recent studies from the APR provide valuable insights into the use of newer AEDS during pregnancy; however, the risks of teratogenic defects (including congenital malformations and cognitive and/or behavioural impairments) and increased seizure frequency during pregnancy are still unclear for most AEDs. The same principle applies to other risks, including pharmacokinetic changes, small-for-gestational-age babies, obstetrical complications, and postpartum depression. Further research is needed to clarify the differential risks of AED use—including specific polytherapy combinations—during pregnancy.

Acknowledgements

K.J.M. presently receives research funding from the NIH NINDS 2R01-NS38455-12 and 3 U01 NS038455-13S1 (Multi-Principal Investigator), PCORI 527 (Co-Principal Investigator), and NIH NINDS 1 R01 NS076665 (consultant).

Competing interests

In the past 10 years, the author has received research funding from Eisai, GlaxoSmithKline, Marius, Myriad, NeuroPace, Pfizer, SAM Technology, Schwartz Biosciences (UCB Pharma), and UCB Pharma. He serves as a consultant for the Epilepsy Study Consortium, which receives monies from multiple pharmaceutical companies. He has consulted on behalf of the Epilepsy Study Consortium for the following companies: Eisai, GW Pharmaceuticals, NeuroPace, Supernus, UCB Pharma, Upsher Smith Laboratories and Vivus Pharmaceuticals. Note that the Epilepsy Study Consortium pays the author's university for his consulting time.

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