

SOME LONG AWAITED ANSWERS REGARDING SEIZURES DURING PREGNANCY

Seizure Control in Antiepileptic Drug-Treated Pregnancy. Vajda FJ, Hitchcock A, Graham J, O'Brien T, Lander C, Eadie M. *Epilepsia* 2008;49(1):172–176. This brief report covers an analysis of 7 years outcome data from the Australian Register of Antiepileptic Drugs in Pregnancy. In studying the control of antiepileptic drug-treated epileptic seizures during pregnancy, it was found that pregnancy had little influence on antiepileptic drug-treated epileptic seizure disorders. Seizures during pregnancy occurred in 49.7% of 841 antiepileptic drug (AED) treated pregnancies in women with epilepsy. Epilepsies that were active in the year before pregnancy tended to increase the risk of intrapartum and postpartum seizures. The risk of seizures during pregnancy was 50–70% less if the prepregnancy year was seizure-free, and decreased relatively little more with longer periods of prepregnancy seizure control. Once there had been 1 year's freedom from seizures there seemed relatively little further advantage in deferring pregnancy to avoid seizures returning while pregnant.

COMMENTARY

The current article is a report from the Australian Pregnancy Registry (APR), and the main points of interest are found in the abstract. The prospective APR is one of several similar trials currently ongoing throughout the world. In addition to the APR, the most significant of these pregnancy registry trials are the European Pregnancy Registry (EURAP), which collects information from 30 different countries, the British Pregnancy Registry, gathering information solely from patients in the UK, and the North American Antiepileptic Drug Pregnancy Registry, which includes patients from the entire USA. There are also pharmaceutical company-sponsored registries both in the United States and in the United Kingdom. The purpose of these registries is to prospectively follow women with epilepsy who become pregnant and then assess the course of their pregnancy and the effects of the condition on the offspring. These registries are designed to provide the best evidence possible on unresolved questions regarding the course of pregnancy for women with epilepsy who are exposed to antiepileptic drugs, including what effects lactation may have on the infant and whether developmental parameters of the offspring are impacted.

The Australian report is the second published registry trial to try to answer two key questions: 1) whether seizures occur less or more frequently during pregnancy and 2) what the effects on the offspring are when seizures do occur. The first study to report to address these issues was the EURAP in 2006 (1); therefore, it is interesting to compare the results of the Australian registry with the European one. In that regard, a variable that needs to be assessed in such an inquiry is whether the serum concentration of the AED is kept stable or varies—does it remain the same during pregnancy as it was before the pregnancy? There are

many examples in the literature, especially with lamotrigine (2,3) and oxcarbazepine (4), that indicate the concentration of the drug drops to about half during pregnancy to then return to the previous level after delivery. Another variable that needs to be addressed is whether patients are compliant and actually take the drugs as directed. Noncompliance is thought to be high during pregnancy, because the mother may think that less of the AED is better for her baby. The EURAP study did indeed discuss both these variables to some extent with the patients (serial serum levels of AEDs were not assessed, however) but not so in the current Australian publication, which is a major limitation of this study. In fact, the APR protocol did not systematically provide for evaluation of AEDs.

The method of recruitment in the APR was for women to call in and register themselves, after being given the pertinent information by their doctor. Therefore, the patient had to take the initiative to make the first phone call, causing a selection bias of patients who were really interested in the project. This recruitment procedure is similar to that of the current North American registry. Recruitment for the EURAP registry, however, was (and still is) instigated by the physician who asks the patient if she wants to participate. After acceptance, the patient is then followed throughout her entire pregnancy. In contrast, once enrolled in the Australian study, patients are first interviewed at the time of recruitment, and then followed up at 4-weeks, 28-weeks, and 1-year postpartum; all interviews were conducted by telephone. Nevertheless, the long follow-up period and the large number of patients who participated in the APR have provided valuable results that can be viewed with optimism. It is now possible to inform patients—in spite of the AED taken or how well regulated the drug levels are—that a powerful predictor of being seizure-free during pregnancy is being seizure-free the year before pregnancy and that, in accordance with the EURAP registry, pregnancy itself does not influence seizure frequency rates in most patients. However, patients who had seizures before

pregnancy continued to have them during pregnancy, labor, and postpartum but did not appear to have an increase in seizures frequency. In the discussion, the authors state that: “In terms of the measures studied, the epileptic process seemed to become “better” no less often than it became “worse” during pregnancy. This conclusion is based on a comparison of events during 9 months of pregnancy with events during 12 months before pregnancy. The same interpretation may not have applied if accurate counts of seizure numbers had been available.”

Similarly, the outcome findings for the offspring in the APR offer some optimism, as the risks in this study for stillbirth or malformations were no higher whether or not the mother had seizures during pregnancy irrespective of seizure type. In the EURAP study, among 1956 pregnancies, there were 36 cases of status epilepticus but only one stillbirth or spontaneous abortion that occurred in close proximity to a seizure. With both registries agreeing on these findings, there seems to be a high probability that having seizures during pregnancy does not affect the offspring, except in rare cases, probably in connection to prolonged seizures.

So what can we learn from these two studies that can help to inform and treat women with epilepsy who become pregnant? As the authors of the ARP point out, patients who have been seizure-free the year before becoming pregnant can be reassured that the risk is low for having new seizures during pregnancy and

delivery—although there is still a chance it could occur. Learning from the EURAP study, patients will benefit from doctors who work diligently to find and maintain the optimal AED intake level before conception and avoid adjustments during pregnancy, unless the serum concentration of the AED declines and needs to be readjusted. Special care is warranted for patients treated with oxcarbazepine and lamotrigine to insure that levels are maintained during pregnancy, thus avoiding exacerbation of seizures. Regardless, all pregnant women with epilepsy need to be closely followed by their neurologist and obstetrician to ensure a successful outcome.

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References

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