

EURAP OUTCOMES FOR SEIZURE CONTROL DURING PREGNANCY: USEFUL AND ENCOURAGING DATA

Seizure Control and Treatment in Pregnancy: Observations from the EURAP Epilepsy Pregnancy Registry

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OBJECTIVE: To analyze seizure control and treatment in pregnant women with epilepsy.

METHODS: Seizure control and treatment were recorded prospectively in 1,956 pregnancies of 1,882 women with epilepsy participating in EURAP, an international antiepileptic drugs (AEDs) and pregnancy registry.

RESULTS: Of all cases, 58.3% were seizure-free throughout pregnancy. Occurrence of any seizures was associated with localization-related epilepsy (OR, 2.5; 1.7 to 3.9) and polytherapy (OR, 9.0; 5.6 to 14.8) and for tonic-clonic seizures, with oxcarbazepine monotherapy (OR, 5.4; 1.6 to 17.1). Using first trimester as reference, seizure control remained unchanged throughout pregnancy in 63.6%, 92.7% of whom were seizure free during the entire pregnancy. For those with a change in seizure frequency, 17.3% had an increase and 15.9% a decrease. Seizures occurred during delivery in 60 pregnancies (3.5%), more commonly

in women with seizures during pregnancy (OR, 4.8; 2.3 to 10.0). There were 36 cases of status epilepticus (12 convulsive), which resulted in stillbirth in one case but no cases of miscarriage or maternal mortality. AED treatment remained unchanged in 62.7% of the pregnancies. The number or dosage of AEDs were more often increased in pregnancies with seizures (OR, 3.6; 2.8 to 4.7) and with monotherapy with lamotrigine (OR, 3.8; 2.1 to 6.9) or oxcarbazepine (OR, 3.7; 1.1 to 12.9).

CONCLUSIONS: The majority of patients with epilepsy maintain seizure control during pregnancy. The apparently higher risk of seizures among women treated with oxcarbazepine and the more frequent increases in drug load in the oxcarbazepine and lamotrigine cohorts prompts further studies on relationships with pharmacokinetic changes. Risks associated with status epilepticus appear to be lower than previously reported.

COMMENTARY

The search to establish the perfect balance between fetal exposure to the harmful effects of antiepileptic drugs (AEDs) and to the harmful effects of seizures requires an understanding of the course of epilepsy during pregnancy. The International Registry of Antiepileptic Drugs and Pregnancy, or EURAP—a prospective, observational pregnancy registry spanning 30 countries—provides the most contemporary large-scale assessment of the course of epilepsy and seizure control during pregnancy. Earlier registries typically selected patients from epilepsy centers, often were retrospective, and used AEDs and management strategies that are no longer current. In contrast, strengths of the EURAP report (1999–2004) are that data were gathered prospectively, it encompasses a wide variety of ethnic groups and clinical settings, and includes patients treated with AEDs that are similar to current prescribing patterns. Although the teratogenic effects of AEDs are well studied and widely

reported, most women with epilepsy nonetheless will need to maintain AED treatment during pregnancy, as control of convulsive seizures is paramount and control of other seizure types is desirable. Uncontrolled seizures during pregnancy have been associated with fetal loss, fetal hypoxia, and poor neurodevelopment.

Many of the findings of this study provide very encouraging news for women with epilepsy, with the majority of patients remaining seizure free throughout pregnancy or having no change in seizure frequency. For those who did change, an almost equal percentage had a decrease in seizures (15.9%) as those who had an increase (17.3%). Seizure control was obtained with monotherapy in the vast majority of the patients (78.7%), thus avoiding the higher fetal risks associated with polytherapy, including major congenital malformations and poor neurocognitive outcomes. Status epilepticus was a relatively rare event (1.8% of pregnancies), with approximately one-third qualifying as convulsive episodes. The rates of maternal and fetal mortality associated with poor seizure control and status epilepticus were lower than previously reported. It is illustrative that the only case of convulsive status epilepticus that resulted in a stillbirth occurred in association with a decrease in AED dosage. Overall,

the stillbirth rate in this study (1.7%) was approximately double the general population in the United States but not out of line with stillbirth rates in other countries (1). Because women were permitted to enroll in the EURAP pregnancy registry up to 16-weeks gestational age, the reported number of spontaneous abortions cannot be used to calculate an accurate spontaneous abortion rate for this patient population. Detailed findings from the study may help improve medical management of women during pregnancy. For instance, deterioration of seizure control occurred equally in the second and third trimesters, and episodes of status epilepticus were spread out evenly throughout pregnancy. If an increase in AED dose or number was required, it was most likely to occur in the second trimester. This outcome is consistent with reports of the enhanced clearance time course of some of the AEDs (2,3). Therefore, waiting until the third trimester to monitor the patient closely is not adequate.

While the findings that the number or dosage of AEDs were more often increased in pregnancies with seizures and in pregnancies using lamotrigine or oxcarbazepine monotherapy are important, they are not particularly surprising. These findings need to be interpreted with caution and do not imply that lamotrigine and oxcarbazepine should be abandoned during pregnancy. In fact, lamotrigine and oxcarbazepine are the only newer generation AEDs with reasonable safety data during pregnancy. Reports of major malformation rates for monotherapy use with lamotrigine vary between 1.0% and 5.6% (4–6) and for oxcarbazepine vary between 0% and 5% (7). Observational studies have indicated that lamotrigine clearance markedly increases during pregnancy (3,8,9), with seizure worsening reported in 45% to 75% of women (8,9). However, multivariate analysis in the EURAP study did not find a higher risk of seizures with lamotrigine monotherapy use, which is encouraging news, especially given the substantial sample size (238 pregnancies). In contrast, the risk of increased tonic-clonic seizures was higher in pregnancies with oxcarbazepine monotherapy; however, this sample size was quite small (41 pregnancies) and confidence intervals were wide. Is it possible that practitioners were more likely to adjust lamotrigine than oxcarbazepine doses prior to seizure deterioration, given the well-known reports of enhanced lamotrigine clearance and the relative lack of data on oxcarbazepine clearance during pregnancy? Approximately 50% of the monohydroxy derivative of oxcarbazepine undergoes glucuronidation, the same route of metabolism as occurs with lamotrigine. Reports of increased oxcarbazepine clearance during pregnancy are beginning to appear (10).

Furthermore, AED treatment was not randomly assigned, and medication choices were likely made according to specific characteristics of the patient, including type of epilepsy, seizure frequency, and past history of failed AEDs. Information was not provided on baseline seizure frequency for the different treatment groups. Details of AED serum concentrations were not

provided in the EURAP study, so it is not clear if and how often active therapeutic drug monitoring was used. Patient compliance, which is known to decrease during pregnancy, could not be objectively assessed. It is not as instructional to combine into one category the patients who had AED dosage adjustments with the patients who had a second AED added, as it is to look at the latter patient group alone. Fetal exposure to additional AEDs likely confers a greater risk for major congenital malformations and poor neurocognitive outcomes than increasing the dosage of an AED to maintain a baseline level—the maternal serum concentration determines fetal exposure, not the oral dosage. The percentage of patients, listed by treatment type, who required adding an AED were as follows: valproic acid 1.4%, carbamazepine 1.8%, polytherapy 3.0%, phenobarbital 3.4%, lamotrigine 4.6%, oxcarbazepine 4.9%, phenytoin 6.8%, and other monotherapies 7.1%. Lamotrigine and oxcarbazepine were not the likeliest treatment groups to require adding an AED.

As in all clinical studies, especially those that require an observational approach, limitations exist in the way the data were collected. While this large study spanned many centers and countries, it was not truly population-based, and almost two-thirds of the participants were from Italy, Scandinavia, and Australia. It also would have been more instructive to capture seizure frequency data beginning prior to conception. Using the first trimester as a reference for seizure control is problematic because many of the factors that can affect seizure control have already been substantially altered (sleep, stress, sex steroid hormone levels, AED clearance, and compliance). Furthermore, enrollment up to 16 weeks gestational age requires that some of the first trimester data are retrospective. Fetal outcomes other than spontaneous fetal loss (e.g., intrauterine growth retardation, premature delivery, major congenital malformations, or neurocognitive outcomes) were not provided, although some of these findings should be forthcoming from EURAP in the near future. In addition, the more frequent requirement for dose or AED addition in the oxcarbazepine and lamotrigine groups should prompt further studies of pharmacokinetic changes during pregnancy, parturition, and the postpartum period. Understanding not only primary pharmacokinetic factors, but also pharmacodynamic alterations, placental metabolism, and placental transport of AEDs may help fill in the gaps to formulate the ideal balance between seizure control and fetal exposure to AEDs. Individual factors, such as seizure type and history, epilepsy syndrome, and pharmacogenomic profile, may help provide more specific predictors for each mother-child pair.

This report from the EURAP pregnancy registry is a very important step toward providing prospective, contemporary information from a variety of sources and sites, regarding the course of epilepsy during pregnancy. It provides useful and encouraging information for women with epilepsy and for their

health care providers. Data from this study will foster better understanding of the impact of pregnancy and its physiologic changes on seizure control and could be used to enhance counseling and treatment of this special patient population to improve outcomes for both the mother and child.

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