ABSTRACT

Certain antiepileptic drugs (AEDs) have been known to incur a higher risk of fetal malformation, but the exact risk and its relation to specific drugs is unknown. Pregnancy registries are the first attempt to systematically study whether any relationship exists between AED use and the frequency or type of congenital malformations. A symposium was held during the 2004 annual meeting of the American Epilepsy Society to discuss the pregnancy registries from the different countries and regions around the world—North America, the United Kingdom, Europe, and Australia. This article presents a summary of each registry's characteristics. Each registry has its own strengths and weaknesses; there are significant differences and similarities, thus the results cannot be pooled. However, patterns emerge as the results become available: the importance of looking for malformations in infants until 1 year of age, the consistently higher teratogenicity of valproate, and the feasibility of an efficient online data collection system across countries, as achieved with one of the international registries. (Adv Stud Med. 2005;5(6C):S585-S588)

More than 1 million women and girls in the United States have seizure disorders, and are most likely taking antiepileptic drugs (AEDs). Many women of childbearing age are taking AEDs for illnesses other than epilepsy, such as migraine, mood disorders, or pain disorders. Although planning for pregnancy is preferred, many pregnancies are unplanned. Most women who become pregnant are concerned about the myriad substances and environments that can adversely affect their fetus. If a woman has a medical condition and is on medication, those fears are magnified.

Certain AEDs are known to incur a higher risk of fetal malformation, but the exact risk and its relation to specific drugs is unknown. Pregnancy registries are an attempt to quickly and systematically study possible associations between exposure to a specific AED and an increased frequency of major malformations. Thus, a worldwide effort has begun to create prospective pregnancy registries for women with epilepsy who are taking AEDs.

A symposium held during the 2004 annual meeting of the American Epilepsy Society discussed the registries from the different countries and regions of the world—North America, the United Kingdom (UK), Europe, and Australia. This article presents a summary of each registry's characteristics. Although the first results from each registry will be published soon, this will be an ongoing project. Each registry has its own strengths and weaknesses; there are significant differences and similarities, thus the results cannot be pooled. However, patterns emerge as the results become available.

Clinicians are concerned about balancing the care for the mother with epilepsy and the care for the growing fetus. At times, those treatment goals may seem contradictory but are never separate. If, as a result of the information from these registries, clinicians can adjust treatment strategies to increase the chances of a
healthy baby, then that information will be vitally important for all women.

**NORTH AMERICAN ANTI-EPILEPTIC DRUG PREGNANCY REGISTRY**

The North American Pregnancy Registry (encompassing the United States and Canada) was established at the Massachusetts General Hospital in Boston in 1997. The primary goal is to determine the frequency of major malformation in infants exposed during pregnancy to one or more AEDs used in the treatment of epilepsy, a mood disorder, or another condition. Women who have completed their pregnancy or women who are planning to become pregnant are not eligible to enroll. The registry staff includes a director/teratologist, epidemiologist, marketing director, consultant neurologist, coordinator, interviewer, and data analyst. A major malformation is defined as a structural abnormality with surgical, medical, or cosmetic importance. Features excluded and defined as not being major malformations are minor anomalies, deformities, physiologic features (such as patent ductus arteriosus heart defect in a premature infant), biochemical disorders (phenylketonuria), neurologic findings (hearing loss), genetic conditions (cystic fibrosis), and chromosome abnormalities (Down syndrome).

A woman can learn about the registry from her doctor, nurse, pharmacist, a friend, or a magazine article. To enroll, she can call the toll-free number (1-888-233-2334), as required by the investigational review board. She is sent a consent form to sign and, if she enrolls, is interviewed by telephone 3 times (at enrollment, at 7 months' gestation, and postpartum). Finally, with the woman's written permission, the registry staff obtains copies of her records from her neurologist and psychiatrist and her infant's doctors. Every 6 months, the major findings are presented by the registry staff in private to the Scientific Advisory Committee, whose members are neurologists, epidemiologists, an obstetrician, and a birth defects specialist. The Scientific Advisory Committee has established criteria for the release of the findings related to specific drugs. In a separate meeting, the Scientific Advisory Committee informs the representatives of each sponsoring company of the decisions made.

To date, approximately 4000 women have been enrolled. Initial results on malformation rates with phenobarbital and valproate, both as monotherapy, have been published.2,3 As with the other registries described in this article, enrollment is slower than desired; power calculations show that a large sample of 555 infants are needed to identify, with 80% power, a 2-fold increase in the frequency of all major malformations. Because most potential enrollees usually begin the conversation with, “My doctor said I should call...,” it is clear that the physician’s enthusiasm for this program makes an important difference in whether the patient will ultimately call for information and enrollment. The Web site with enrollment information for this registry is www.aedpregnancyregistry.org.

**UNITED KINGDOM EPILEPSY AND PREGNANCY REGISTRY**

The UK Registry began in 1996 in Belfast, Northern Ireland. The initial design was to include only newer AEDs, but this design was ultimately extended to include all AEDs. The primary objective is to estimate the relative risks of major congenital malformations between each of the AEDs. The secondary objective is to look for any patterns of malformation associated with drug exposure based on dose, risk of seizures, and use of folic acid. As with the other registries, it is a prospective, observational study.4,5

Pregnancies in women with epilepsy are included if the outcome of the pregnancy is not yet known. AED use can be as monotherapy or polytherapy. The information is collected primarily at 2 stages. At registration, demographic details are collected (ie, gestational age at the time of registration, epilepsy history, type of epilepsy, etiology, onset, and presence of seizures during pregnancy [specifically, during the first trimester], AED type and dose before and during pregnancy, AED changes for that period, and folic acid exposure). At 3 months after delivery, information is collected from the general practitioner (GP) regarding family history, prenatal testing details, pregnancy outcome details (ie, gestation, sex, weight, delivery method, and birth defect details), and postnatal problems. In the UK, the GP is the repository for all of a patient’s information. All information from every specialist seen by the patient is sent back to the GP. In this study, if any questions arise about the patient’s information, the specialist is contacted directly. A major congenital malformation is defined as an abnormality of essential embryonic structure requiring significant therapy, which is present at birth or discovered during the infant’s first 3 months. This definition is from the
European Surveillance of Congenital Anomalies grading system.6

Women can enroll directly or through physician referral. To date, more than 4000 women have been enrolled, with 722 ongoing pregnancies. Most of the women are administered monotherapy; approximately 21% have polytherapy. The most common AEDs used thus far are carbamazepine, valproate, and lamotrigine. Phenobarbital is rarely prescribed in the UK; a small number of patients are taking phenytoin. Information on this registry can be found at www.epilepsyandpregnancy.co.uk.

**EUROPEAN PREGNANCY REGISTRY**

The International Registry of AEDs and Pregnancy (EURAP; formerly the European Registry of AEDs) was launched in 1999 in Sweden and in Italy. Today, 40 countries participate, with approximately 330 reporting physicians. The primary goal of EURAP is to compare the risk of major congenital malformations following maternal intake of AEDs and their combinations. This is an observational study, thus results or participation do not interfere with the medical management of the pregnant woman nor the physician's decision on which treatment to use. Secondary objectives of EURAP include the evaluation of any specific pattern of fetal abnormalities, dose-effect relationships, and the extent to which other risk factors may contribute to malformations.

Pregnant women are enrolled before the outcome of the pregnancy is known and never later than gestational week 16, to avoid reporting bias. Of note, later-stage pregnancies also may be enrolled but are considered in a separate retrospective analysis; they are not included in the overall risk assessment. Pregnancies with AED exposure at the time of conception are included, irrespective of the indication for treatment, although the enrollment of women for nonepilepsy indications has to date remained small (approximately 1%). There is no internal control group of untreated women with epilepsy.

Assessments are performed at each trimester, after birth, and also 1 year following birth. All data are recorded online prospectively in case report forms. A national coordinator in each country reviews the reports to ensure full and accurate completion and then forwards the report to the central registry in Milan, Italy. The teratogenic endpoint is the presence or absence of major congenital malformations; however, physicians are encouraged to report and record any observed changes or characteristics that they consider to be abnormal. The Central Outcome Classification Committee decides whether the reported abnormality is a major congenital malformation and classifies the subtype of malformations. Members of this committee are blinded as to the type of exposure.

As of January 2005, approximately 6000 women have been enrolled, with an enrollment rate of approximately 150 new pregnancies per month. Fewer than 20% of the women are retrospective pregnancies; some have to be excluded for several reasons (eg, did not meet inclusion criteria, loss to follow-up, major change in drug therapy during pregnancy, or unclear malformations), and approximately 50% are ongoing pregnancies or pending reports waiting for completion or correction.

The most commonly used monotherapy in this cohort thus far is carbamazepine, followed by valproic acid, lamotrigine, and phenobarbital. To date, the results show that 29% of malformations were detected by ultrasound during pregnancy (2% in stillbirths; 48% at birth). However, 29% of the malformations were not detected until the follow-up appointment at 1 year after birth. One case also had an additional defect detected when the infant was 1 year old.7

The first interim classification will analyze the most common monotherapies and polytherapy as one group. Although the initial malformation rates will be published soon, specific rates by different AEDs will not be reported until a larger number of pregnancies are enrolled. The women were not randomly assigned to treatment, and the physician selection of a specific AED for an individual woman may, in some way that is not yet understood, be linked to other risk factors for birth defects. A higher malformation rate is not firm evidence for a causal relationship between that exposure and the outcome. Multiple regression analysis will consider each AED and possible confounders, such as family history of malformations, history of abortions, type of epilepsy, maternal age, and convulsive seizures during the first trimester. Information on this registry can be found at www.eurapinternational.org.

**AUSTRALIAN PREGNANCY REGISTRY**

Similar to the EURAP registry, the Australian registry was founded in 1999 and its design is largely the same as the EURAP registry.4,5 The primary objective
is to evaluate the incidence of fetal malformations from pregnancies exposed to AEDs. Secondary objectives are to determine if certain AEDs or combinations are associated with a higher incidence or specific type of adverse pregnancy outcome, to determine the influence of the seizures, the epilepsy syndromes, the genetic background, and environmental factors on birth outcome, and to study the comparative efficacy of AEDs on seizure protection in pregnancy.

Women taking AEDs for other indications are also included, as are a small number of women not taking AEDs. Anyone (eg, the patient herself, physician, or midwife) can make the first phone call to begin enrolling the patient. However, the patient is not actually enrolled until the registry contacts her to confirm her interest in participation and the patient signs a consent form. Women are included before the birth outcome is known. Upon enrollment, women are interviewed at enrollment (preferably at 3–4 months' gestation), at 7 months' gestation, at birth, and then at 1 year.

To date, almost 700 women have been enrolled with almost 600 of the pregnancies reaching completion. Information on this registry can be found at www.victorianepilepsycentre.org.au/.

**NEURODEVELOPMENTAL EFFECTS OF ANTIPILEPTIC DRUGS**

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) is a different type of registry than the others described in this article. The NEAD goal is to observe children (until 6 years of age) who are born to mothers taking AEDs (for epilepsy, as monotherapy) to assess the cognitive and behavioral outcome effects of the drugs (as opposed to anatomical defects). The NEAD is a prospective study that is the result of merging 2 parallel studies started in the UK and the United States, encompassing one UK center and 24 US locations. Pregnant women are included if they have partial or primary generalized epilepsy and are taking carbamazepine, lamotrigine, phenytoin, or valproate as monotherapy. These are the 4 most commonly used AEDs in the participating tertiary medical centers and, as with the other registries, carbamazepine is the most frequently used drug. To date, nearly 400 women have been enrolled.

The original primary outcome of interest was the child's IQ and predicted IQ based on the parents, in addition to several other cognitive measures. However, the registry also tracks serious adverse events (death, major congenital malformation, and developmental delay). More information on this registry can be found at www.neuro.mcg.edu[np/nead.htm.

**CONCLUSIONS**

These registries offer the most useful information to increase the chances of a healthy pregnancy outcome for women of childbearing age who are taking AEDs. There are important differences among the registries, thus pooling their data will be difficult, and what is determined to be statistically significant may be different from what the mother considers to be clinically significant.

Several important trends from these registries already have been noted: the importance of looking for malformations until the child is 1 year of age, the consistently high teratogenicity of valproate, and the feasibility of an efficient online data collection system across countries, as is achieved with EURAP.

The Epilepsy Foundation of America also has information for patients on understanding pregnancy registries (www.epilepsyfoundation.org/epilepsyusa/media/understandregistries.cfm).

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