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## **The New Antiepileptic Drugs and Pregnancy**

Volume 11, No.3, August 2004

This issue of Risk Newsletter explores the current data on the following second generation antiepileptic drugs (AEDs): Lamictal, Trileptal, Topamax, and Neurontin.

About 1 in every 200 pregnant women has epilepsy, and up to 35% of women with epilepsy have increased seizure activity during pregnancy (AAN, 1998). The latter may be due to changes in sex hormones, metabolism, sleep patterns, or medication compliance (Morrell, 2003). The majority of these pregnancies have normal outcomes; however, there are specific maternal and fetal concerns related to uncontrolled seizures. While studies are not conclusive, seizures during pregnancy have been associated with such obstetrical complications as prematurity and stillbirth (Morrell, 2003, AAN, 1998). Seizures can result in maternal and fetal hypoxia and acidosis, which potentially could lead to neurological damage or be life-threatening. Therefore, treatment during pregnancy is typically instituted when a woman has a history of seizures within the past 24 months. If therapy is to be withdrawn during pregnancy, it is ideally attempted 6 months prior to conception to allow time to evaluate for seizure recurrence (AAN, 1998).

The risk for congenital malformations ranges from 4-10% following monotherapy treatment with older, "first generation" AEDs (Dolk and McElhatton, 2002). This is a 2- to 3-fold increased risk compared to the general population. Although this increased risk was once thought to be due to the underlying maternal seizure disorder, it is now largely attributed to the use of AEDs (Holmes et al., 2001). A woman's risk for congenital anomalies increases with polytherapy (AAN, 1998). Therefore, monotherapy treatment with the medicine most effective for the specific seizure type is preferred.

Second generation AEDs have been available since 1993. Unfortunately, these medications have not been well studied and, consequently, risks to the fetus are largely unknown. Of studies that have been published, major malformations is the only outcome variable evaluated. Studies have not been conducted to determine if there are any patterns of minor malformations or developmental impairment (i.e., anticonvulsant embryopathy).

Lamictal (generic name: lamotrigine)

For second generation AEDs, the largest dataset on pregnancy outcomes is available for lamotrigine (LTG), a medicine chemically unrelated to the first generation AEDs. While LTG decreases fetal folate levels in rats, it does not decrease human adult blood folate levels (GlaxoSmithKline, 2004). It is not known if human fetal folate levels are altered with LTG or whether higher maternal folic acid supplements (4-5 mg daily) is beneficial for women taking Lamictal.

Marchi et al., (2001) treated pregnant rats during organogenesis with four times the recommended human dose of LTG. Offspring demonstrated low birth weight and altered brain structure, which included increased volume and diameter of the cerebral structure, increased density of the subcortical

layer, and ventricle dilation (Marchi et al., 2001). The relevance of these findings to human pregnancy is unknown. Experimental animal studies by the manufacturer did not find an increase in congenital malformations associated with LTG (GlaxoSmithKline, 2004).

Sabers et al., (2004) reported on the outcomes of 147 human pregnancies with various AED exposures. Seventy-four percent of the total group were on monotherapy AED treatment, and 80% of the total group took folic acid supplements, with the majority taking 5 mg daily. Of the total group, 35% were treated with LTG. For monotherapy treatment with LTG, there were no major malformations. There was one case of a ventricular septal defect in a LTG exposed pregnancy also treated with oxcarbazepine.

The largest dataset on LTG exposure during pregnancy has been collected by the manufacturer's pregnancy registry. This is a voluntary, noncontrolled prospective registry with 20-30% of women lost to follow-up. As of March 2003, the registry had outcomes for 414 first trimester exposures to LTG monotherapy. There were 12 infants with major malformations for a rate of 2.9%. The spectrum of birth defects observed and the proportion of malformations were not different from the baseline risks. This sample size was sufficient to detect, with 80% power, a 1.79-fold increase in the proportion of major birth defects. Additionally, an abstract from the United Kingdom Lamictal registry reported on 390 first trimester pregnancy exposures. There were 8 major malformations for a malformation rate of 2.1%, which was within the rate present in the general population (GlaxoSmith Kline, 2004).

Based on available data, LTG does not appear to significantly increase the chance for congenital anomalies. Long-term data regarding any possible neurobehavioral effect of LTG exposure in utero is not available.

Trileptal (generic name: oxcarbazepine)

There were no significant increases in congenital anomalies when pregnant mice were treated with 20-46 times the human dose of oxcarbazepine (OXC) (Bennett et al., 1996). However, studies conducted by the manufacturer demonstrated increased craniofacial, cardiovascular and skeletal malformations in rats treated during organogenesis with 1.2 times and 4 times the maximum recommended human dose of OXC. In rabbits, there was an increase in fetal loss but no teratogenicity associated with OXC administration at 1.5 times the maximum human dose (Novartis Pharmaceuticals, 2004).

Reports on human pregnancy exposure to OXC are limited and most studies do not specify whether the women were on OXC monotherapy or polytherapy. In one study with 12 pregnancies exposed to OXC during the first trimester, three pregnancies resulted in miscarriage, while nine pregnancies resulted in newborns without structural malformations (Friis et al., 1993).

Another study of 37 women exposed to OXC, alone or in conjunction with other AEDs, demonstrated two cases of ventricular septal defects. One case was exposed to OXC alone and the other was exposed to OXC and LTG, as mentioned previously (Sabers et al., 2004).

Additional reports specifying OXC monotherapy during the first trimester total 13 pregnancies, one of which resulted in an unspecified malformation (Kaaja et al., 2003; Wide et al., 2004). Meischenguiser et al., (2004) reported on the Argentinian experience of 35 monotherapy exposures with no major congenital anomalies. There was also one cardiac anomaly with 20 cases of OXC polytherapy (Meischenguiser et al., 2004). In the case of the cardiac anomaly, the pregnancy was exposed to 1200 mg OXC and 150 mg phenobarbital. Since the numbers of pregnancies are small, it cannot be known whether the reported physical birth defects were due to OXC or to other factors.

It should be noted that OXC is a derivative of carbamazepine (brand name: Tegretol), a first generation AED and folate antagonist. Carbamazepine is associated with a 6.5% congenital malformation rate and a 1% chance for neural tube defects (Wide et al., 2004). Based on what is known about carbamazepine,

maternal serum AFP screening, targeted fetal ultrasound and fetal echocardiogram should be performed in pregnancies treated with OXC.

Topamax (generic name: topiramate)

Topiramate (TPM) is structurally and pharmacologically different from other classes of AED (Ohman et al., 2002). According to the manufacturer, when TPM was administered to pregnant mice, rats and rabbits during organogenesis, increased fetal mortality and teratogenic effects were observed at doses lower than the recommended human dose. Craniofacial and limb malformations were seen most frequently. These malformations were consistent with malformations observed in animals treated with similar medications, the carbonic anhydrase inhibitors. However, since these malformations have not been observed in humans treated with other carbonic anhydrase inhibitors, the manufacturer suggests these effects may be species-specific (Ortho-McNeil Pharmaceutical Communication, 2003).

In the case of TPM, human reproductive data is limited to individual case reports and small case series. A report of 5 pregnant women on TPM polytherapy revealed no congenital malformations at delivery (Öhman et al., 2002). A postmarketing survey by the manufacturer noted that there were 10 pregnancies treated with monotherapy and no congenital malformations identified (Ortho MacNeil Pharmaceutical Communication, 2003).

There is a single case report of an in utero exposure to 1400 mg daily of TPM throughout gestation that resulted in an infant with multiple minor anomalies comprising of hirsutism, third fontanelle, anteverted nares, nail hypoplasia and consistent with the effects seen with first generation AEDs (Hoyme et al., 1998). Additionally, the manufacturer noted that they had received case reports of hypospadias (Ortho MacNeil Pharmaceutical Communication, 2003). No causal relationship could be established with this type of data. Due to the limits in available human reproductive data, fetal risks have not been determined following TPM exposure.

Neurontin (generic name: gabapentin)

A study in mice, rats, and rabbits did not observe any developmental toxicity of gabapentin (Petrere and Anderson, 1994). However, the manufacturer noted that offspring of mice and rats treated with one to four times the recommended human dose of gabapentin (GBP) had delayed ossification of several skeletal bones. Studies on rabbits demonstrated increased fetal loss rates at one-fourth the maximum human dose but no increase in malformations (Pfizer Pharmaceuticals, 2004).

A post-marketing surveillance study of GBP included 11 pregnancy outcomes with first trimester GBP exposure. No congenital abnormalities were observed (Wilton and Shakir, 2002).

The Boston GBP registry collected a combination of retrospective and prospective reports to comment on 51 pregnancies with 44 livebirths. Monotherapy accounted for 33% of the cases, and 81% of the pregnancies were exposed to GBP throughout pregnancy. There were two major congenital anomalies (one complicated with valproate) for a major malformation rate of 4.5% (Montouris, 2003). Due to small sample size, this is considered a very tentative estimate.

## **Summary**

Lamictal is the only second generation AED with sufficient reproductive data suggesting it does not significantly increase the chance for congenital anomalies. Information on possible longterm neurobehavioral effects however is pending.

Antiepileptic Drug Registry

More studies are needed to assess the risks of AED use during pregnancy since discontinuing medication is not an option for most women with epilepsy. The Genetics and Teratology Unit at Massachusetts General Hospital has established the first US hospital-based AED registry. The purpose of the registry is to provide a faster method for establishing the effects of each AED during pregnancy

and to provide better counseling and management to pregnant women with epilepsy.

Ascertaining whether a medication has detrimental effects requires large numbers of pregnant women. About 400 women taking a single AED must be enrolled before any study can statistically identify a doubling of the baseline risk for physical birth defects. Many more women are needed to detect more subtle effects of any medication. This AED registry does not release outcome data until statistical significance is reached. Although this has been a source of frustration for health care professionals, the risk of major malformations in various series of 25 birth outcomes has ranged from 3% to 35% for the same AED (Holmes, 2004 OTIS update). Therefore, the registry does not want either to falsely reassure or falsely alarm until the data is statistically significant.

Health care professionals can obtain more information about the AED registry by calling 1-888-233-2334, or visiting <http://www.mgh.harvard.edu/aed/> Physicians can refer interested women to these same contacts, but only pregnant women can enroll themselves in the registry.

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