



Antiepileptic Drug Pregnancy Registry

WINTER 2007

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Folic Acid and Antiepileptic Drug Interaction

In the general population, when a woman takes a daily multivitamin tablet with folic acid just before and at conception, her risk of having a child with spina bifida and other birth defects is decreased^{1,2}. However, for women taking AEDs, it is not yet clear if taking a daily multivitamin with folic acid will decrease their risk of having a baby with a birth defect. One concern is that some anticonvulsant drugs, like phenytoin (Dilantin®) and carbamazepine (Tegretol®) are folic acid antagonists, meaning that they counteract the effects of folic acid supplements³. But, some other AEDs, like lamotrigine (Lamictal®) are not folic acid antagonists³.

Very few research studies have addressed this issue. In one study, researchers at Boston University⁴ showed that folic acid supplements did not affect the risk for heart defects, oral clefts or urinary tract anomalies in children born to mothers taking some AEDs. However, in that same study these researchers found that taking a folic acid supplement decreased the risk for spina bifida in infants born to women taking carbamazepine (Tegretol®)⁵. *(continued on page 2)*

A Message from the Registry

We thank everyone who has enrolled in the Registry! Your participation has been invaluable to our task of determining the fetal risks associated with AED use during pregnancy. Your commitment is vital to our goals, and the information you provide will be useful in counseling pregnant women in the future. THANK YOU!

We are beginning a busy time at the Registry. In 2007, we will release the findings in the infants of all mothers who had taken only one drug during their pregnancies. The release of this data could impact the choices made by women and their doctors in the future.

To accomplish this ambitious goal, we need complete files for every woman who has enrolled in the Registry. For our analyses, we only will be able to utilize information from women who have complete files. Even if you delivered your child months or even years ago, the information regarding your pregnancy is still valuable to the Registry! Allowing the release of your medical records and completing your final interview provides the Registry with the best understanding of AEDs and their effects on babies.

We may contact you to finish a 5-minute phone interview, or to collect some additional paperwork in order to complete your file. We will provide you with easy instructions for filling out forms, downloadable forms on our web site, and postage-paid return envelopes. Please look out for our mailing! If you have any questions, please do not hesitate to contact us TOLL FREE at **1-888-233-2334**. As always, the information you give us is strictly confidential and is not accessible to anybody outside of the Registry staff. Thank you again for your participation.

The Registry Staff

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Unfortunately the findings released by the North American AED Pregnancy Registry do not suggest that folic acid supplements prevent the occurrence of the major malformations identified. All mothers taking valproate and whose infants had a major malformation, as reported by Wyszynski et al⁶, had been taking a folic acid supplement at conception. In the recent report of significant increased risk for cleft lip or cleft palate in those infants born to women taking lamotrigine (Lamictal®), all five mothers had been taking a folic acid supplement of at least 3.0mg per day at conception⁷.

According to Morrell, there are no negative side effects of taking folic acid supplements with AEDs, and today's epileptologists have dispelled the decades-old myth that large doses of folic acid supplements may weaken the efficacy of AEDs³. Modern medicine has also rejected the suspicion that folic acid supplements could promote seizures.

At this time it is recommended that all women of childbearing age taking AEDs receive folic acid supplementation at 4.0 to 5.0 mg per day⁸. It is crucial to stress the importance of taking a vitamin supplement with folic acid at the time of conception. It is not nearly as helpful to start taking vitamins with folic acid after you know you are pregnant. Since half of all pregnancies are not planned, it is recommended that women take a folic acid supplement continuously throughout their childbearing years.

REFERENCES:

¹ Wald N.J. Folic Acid and the prevention of neural-tube defects. *N Engl J Med*, 2004; 350:101-103. ² Botto L.D., et al. Vitamin supplements and the risk for congenital anomalies other than neural tube defects. *Am J Med Genet (Part C)* 2004; 125C:12-21. ³ Morrell M.J. Folic Acid and Epilepsy. *Epilepsy Currents*, 2002; 2:31-34. ⁴ Hernandez-Diaz S., et al. Folic Acid Antagonists During Pregnancy and the Risk of Birth Defects. *N Engl J Med*, 2000; 343:1608-1614. ⁵ Hernandez-Diaz S., et al. Neural Tube Defects in Relation to Use of Folic Acid Antagonists during Pregnancy. *Am J Epidemiol*, 2001; 153:961-968. ⁶ Wyszynski D.F., et al. Increased rate of major malformations in offspring exposed to valproate during pregnancy. *Neurology* 2005; 64:961-965. ⁷ Holmes L.B., et al. Increased Risk For Non-Syndromic Cleft Palate Among Infants Exposed To Lamotrigine During Pregnancy. *Birth Defects Research (Part A)* 2006; 76:5. ⁸ Wilson R.D., et al. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can.* 2003 25:959-73.

Are you moving? Have a new phone number?

If any of your contact information has changed, or will change before the birth of your baby, please let the Registry know. It is helpful for us to have your updated contact information so that we can more easily complete your file and notify you of any new research findings.

To report any changes made since your last interview, please call us TOLL FREE at **1-888-233-2334**. Thank you!

Statistics Update

Enrollment: 5525 participants as of November 2006

Participants:

Gravidity:

1st Pregnancy: 38%
2nd Pregnancy: 30%
3rd Pregnancy: 17%
4th + Pregnancy: 16%

Education:

Some high school or less: 21%
Some college: 25%
College: 34%
Post-graduate: 21%

Ethnicity:

White: 86%
Black: 4%
Hispanic: 6%
Other: 4%

Health Insurance

Some form of insurance: 97%

Drugs Taken:

23 different monotherapies and 197 different polytherapy combinations

Medications being Studied by the AED Pregnancy Registry *:

alprazolam (generic)
Ativan® (lorazepam)
Carbatrol® (carbamazepine)
Celontin® (methsuximide)
Depakene® (valproic acid)
Depakote® & Depakote ER (divalproex sodium)
Diamox® (acetazolamide)
Dilantin® (phenytoin)
Felbatol® (felbamate)
Frisium® (clobazam)
Gabitril® (tiagabine)
Keppra® (levetiracetam)
Klonopin® (clonazepam)
Lamictal® (lamotrigine)
Lyrica® (pregabalin)
Mesantoin® (mephenytoin)
Milontin® (phensuximide)
Mysoline® (primidone)
Neurontin® (gabapentin)
Paradione® (paramethadione)
Peganone® (ethotoin)
phenobarbital (generic)
Phenytek® (extended phenytoin sodium)
Sabril® (vigabatrin)
Serax® (oxazepam)
Tegretol® (carbamazepine)
Topamax® (topiramate)
Tranxene® (clorazepate dipotassium)
Tridione® (trimethadione)
Trileptal® (oxcarbazepine)
Valium® (diazepam)
Zarontin® (ethosuximide)
Zonegran® (zonisamide)

* This is not a complete list. Please call TOLL FREE 1-888-233-2334 to determine if the Registry is studying your specific medication.

Congratulations to our Raffle Winners!

We are pleased to announce the winners of our most recent control group raffle drawing. The referring participant winner of the \$400 American Express Gift Card is **C. from North Carolina**. The winner of the control group raffle, who also receives a \$400 American Express Gift Card, is **D. from California**.

The Registry is continuing to recruit women to participate in our control group. Our sincere appreciation and thanks to those of you who have already referred controls to the Registry. **But we still need your help!** If you know someone who could serve as a control, please ask her to call us TOLL FREE: 1-888-233-2334. In order to participate as a control, a woman must currently be pregnant and not taking any antiepileptic medication of any kind.

For every friend or family member you refer who enrolls as a control with the Registry, you will be entered in a drawing to win a \$400 **American Express Gift Card!** In addition, each control group participant will also be entered into a separate drawing to win a \$400 **American Express Gift Card**. You both get a chance to win! Even if you have already referred one friend, you can refer another! The more controls you refer, the better your chances are of winning the great prize! If you have any questions, please call us TOLL FREE at 1-888-233-2334.

New research study needs your help

Researchers at the University of Massachusetts need your help in studying learning and language in infants and toddlers **exposed to valproate** before birth. We are also looking for women who did not take medication during their pregnancy to participate in our comparison group. Participants are paid \$50.00 for a 2-hour appointment either at our lab or at a convenient location closer to your home. If you would be interested in learning more, please contact Dr. Jane Adams at Jane.Adams@umb.edu or (617) 287- 6346.

AED Pregnancy Registry

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The Publications of the Registry

Holmes L.B., Wyszynski D.F., Baldwin, E.J., Habecker, E., Glassman, L.H., Smith, C.R. Increased Risk For Non-Syndromic Cleft Palate Among Infants Exposed To Lamotrigine During Pregnancy. *Birth Defects Research (Part A)* 2006; 76:5.

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Who Can Participate in the Registry?

The Registry is currently enrolling pregnant women who are taking AEDs for any reason. Participating in the Registry only requires 3 telephone interviews of about 10 minutes each, and all information is kept strictly confidential. We are also recruiting controls, please see page 3 for details. Enrollment is open to women during any stage of pregnancy, but not after the birth of the infant. Ideally, the Registry would prefer to enroll women before they reach the 16th week of pregnancy, or before any prenatal screening. To enroll, or get more information please call the Registry TOLL FREE at **1-888-233-2334**.

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