



Antiepileptic Drug Pregnancy Registry

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Getting It Right for the Child: Neurodevelopment

By Kimford Meador MD, Melvin Greer Professor of Neurology, University of Florida

In utero antiepileptic drug exposure can produce behavioral deficits in animals, and this occurs at blood levels similar to therapeutic levels in humans^{1,2}. It is known that there is an increased risk of abnormal functional neurodevelopment in children born to women with epilepsy. Some of this risk may be attributed to AEDs. A number of studies have been initiated in order to investigate this further.

A retrospective study of women in the UK between the ages of 16 and 40 examined the relative risks of additional educational needs (AENs) in children exposed to AED monotherapy or polytherapy in utero. The results showed that 30% of school age children exposed to valproate monotherapy in utero had AENs, compared to 3.2% and 6.5% of those exposed to carbamazepine and other monotherapy groups, respectively³.

A second study from the same center has recently been conducted involving a neuro-psychological investigation of 249 children between the ages of 6 and 16, exposed to AEDs in utero. Results showed that children exposed to valproate had a significantly lower verbal IQ when compared to children exposed to other AEDs, or not exposed at all. The same children, exposed to valproate, were more likely to have an IQ below 69 and memory impairment when compared to the other groups⁴. (*continued on page 2*)

Most Recent Publication of the Registry

Evidence of Increased Birth Defects in the Offspring of Women Exposed to Valproate during Pregnancy

Data were collected by the Antiepileptic Drug (AED) Pregnancy Registry from pregnant women throughout the U.S. and Canada who were taking an anticonvulsant drug. The prevalence of congenital malformations among offspring of monotherapy VPA exposed women was compared to that among infants of women exposed to all other AEDs ("internal comparison group"), and to that among newborns in the Active Malformations Surveillance Program at Brigham and Women's Hospital ("external comparison group").

Sixteen affected cases were identified among 149 VPA exposed women (proportion: 10.7%, 95% confidence interval [CI]: 6.3-16.9%). The prevalence in the internal comparison group was 2.9% (95% CI: 2.0-4.1%; odds ratio: 4.0, 95% CI: 2.1-7.4; $p < 0.001$). Assuming a 1.62% prevalence in the external comparison group, the relative risk to having an affected offspring for VPA-exposed women was 7.3 (95% CI: 4.4-12.2; $p < 0.001$).

Maternal exposure to VPA during the first trimester of pregnancy increases significantly the risk of major malformations. Teratogenic risk should be a factor when selecting therapy for women of childbearing age.

Wyszynski DF *et al.* Neurology 2005 (in press)

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Getting It Right For The Child (continued from Page 1)

Preliminary results from a prospective Finnish study support the observation of poorer outcomes with valproate. The investigators tested 60% of 299 children of mothers with epilepsy and 50% of 277 children of healthy control mothers who have been followed since birth. The mean verbal IQ score following in utero exposure to valproate was 82 and to carbamazepine was 96, compared with 95 for the healthy controls⁵.

The NEAD study (www.neuro.mcg.edu/np/NEAD.htm) represents a prospective investigation of patients in the UK and USA funded in part by the NIH⁶. To date, over 300 pregnancies have been recorded, examining the effects of the four most commonly used AEDs (carbamazepine, lamotrigine, phenytoin and valproate), when used as monotherapy, on the long-term cognitive and behavioral development of the child. The percentages of children with serious adverse outcomes (i.e. neurodevelopmental delay, major congenital malformations, or fetal death) for each AED were: carbamazepine 9%, lamotrigine 1%, phenytoin 11% and valproate 24%, suggesting that the risks differ significantly across the different AEDs⁷.

Studies in this area are preliminary. Each study has limitations, but together they suggest that there is a greater risk for valproate. The studies emphasize the importance of understanding the neurodevelopmental effects of AEDs on children born to mothers with epilepsy.

REFERENCES: ¹ Adams J *et al.* Neurotoxicol Teratol 1990;12:203-214 ² Finnell RH *et al.* Reprod Toxicol 1991;5:281-299 ³ Adab N *et al.* J Neurosurg Psych 2001;70:15-21 ⁴ Adab N *et al.* J Neurosurg Psych 2004;75:1575-1583 ⁵ Failey E *et al.* Epilepsia 2002;43(suppl 8):56 ⁶ NEAD = Neurodevelopmental Effects of Antiepileptic Drugs; NIH=National Institutes of Health ⁷ Meador K *et al.* unpublished data

(Reprinted with permission from "Getting It Right First Time", a 2004 publication of GlaxoSmithKline)

A Message from the Registry Staff

Thank you for participating in the Registry. As a Registry Participant you are helping us to gather critical information about taking Antiepileptic Drugs during Pregnancy. As you know, participation in the Registry involves only three simple telephone interviews – two during your pregnancy and one after your baby is born. Of course, after a baby arrives, life can change very quickly. Days (and nights) tend to become extra busy and sometimes relocation to a new home follows. While inevitable, this can make it difficult for our staff to contact you for your post-partum interview. This interview is critical as it is the only way we can learn about your baby's health and status after you deliver. Normally we try to call you within 3-4 months after delivery based on the anticipated day you provided us at enrollment.

Therefore, if you have **not** completed a post-partum interview with us and the timeframe has exceeded 4 months from your delivery (and/or your contact information may have changed) we would greatly appreciate it if you would call us toll-free at **1-888-233-2334**. If regular business hours are not convenient, you may leave a message stating your name, telephone number and a good time and day to call, including weekends. The interview takes less than 10 minutes and the information you share will continue to help women like yourself in the future. We look forward to speaking with you soon!

Statistics Update

Enrollment:

3840 participants as of November 2004

Participants: (range is for the five most commonly used anticonvulsants)

Ethnicity:

White: 85.9% - 93.6%

Black: 2.4% - 4.8%

Hispanic: 2.8% - 7.3%

Education:

<12 yrs 18.6% - 27.8%

>12 yrs: 78.9% - 87.9%

Gravidity 1 or 2:

69.4% - 74.4%

Private Insurance

76.6% - 89.1%

Drugs Taken:

23 different monotherapies and 197 different polytherapy combinations

Breastfeeding: Information about the "new" AEDs

By Gideon Koren, M.D., Director, Motherisk Program, Toronto, Ontario

As more new antiepileptic drugs enter the clinical arena, more women will use them in the postpartum period. With the major drive to encourage breastfeeding due to obvious advantages of breastfeeding, young mothers taking these new drugs wish to know whether it is safe to breastfeed. These mothers have three options: 1) To stop the drug so the baby is not exposed to the "unknown". This option may be highly problematic if the mother is well controlled on the medication. 2) To discontinue breastfeeding and take the medication. This approach will deny the baby the potential benefits of breastfeeding. It is important to stress, though, that millions of healthy babies have been doing well on formula. 3) To continue the medication and breastfeed.

The Motherisk program in Toronto is dealing with about 160 calls a day on drugs in pregnancy and 40 calls on drugs in breastfeeding. The first information on drug excretion in milk comes typically in the form of single measurements in single patients. In a systematic review we conducted in 2003, less than 60 medications had a scientifically sound pharmacokinetic description of the amount of medication accumulated in milk. For several hundred other drugs the information is partial or negligible¹. One can follow up the child for adverse events without necessarily measuring milk levels.

Several research groups have tried to predict how much drug will enter the milk based on the physico-chemical characteristics of the drug: molecular weight, lipophilicity and pK (the pH at which half of the drug is ionized). However, as shown by us, this method has poor predictive value¹⁻². Presently there is little or no evidence as to how much of the new antiepileptics get into milk. Yet the available data suggest that the amounts are way below the 10% standardized maternal dose (i.e. how much of the drug is offered to the baby through milk as compared to the amount per body weight given to the mother).

For more information about Motherisk, please visit www.motherisk.org.

REFERENCES: ¹ Larsen LA, Ito S, Koren G: Prediction of milk/plasma concentration ratio of drugs. Ann Pharmacother 2003;37:1299-306 ² Koren G, Ito S, Larsen LA. Authors' reply. Ann Pharmacother 2004;38:176

Medications being Studied by the AED Pregnancy Registry *:

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)
 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)
 Xanax® (alprazolam)
 Zaronin® (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.

AED Pregnancy Registry

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We're on the Web!

Visit us at:

www.aedpregnancyregistry.org

1-888-233-2334

CALL TOLL-FREE



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

You Could Win a \$400 prize!

The AED Registry is continuing its campaign to recruit a control group (or comparison group) for the Registry. Any of your friends or family members who are currently pregnant and are NOT taking any antiepileptic medications are eligible to participate. Being in the control group is easy - there are only 3 short phone interviews, each taking less than 10 minutes. For every friend or family member who enrolls as a control with the Registry, you will get a chance to win the prize of your choice. And, your friend will be entered in a separate raffle to win her choice of the same prizes. You can BOTH win! Each prize option is worth \$400! You can learn more about these prizes on our web site at www.aedpregnancyregistry.org. If you know someone who could serve as a control, please ask her to call us toll free at **1-888-233-2334**.

Who Can Participate in the Registry?:

The Registry is currently enrolling pregnant women who are taking anticonvulsant medication for any reason. Participating in the Registry only requires 3 telephone interviews of about 10 minutes each, and all information is kept strictly confidential.

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 they have had any prenatal screening. To enroll, or get more information please call **1-888-233-2334**.

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