

What can we say to women of reproductive age with epilepsy?

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It is not yet established which antiepileptic drugs (AEDs) are most likely to allow an uncomplicated pregnancy and delivery of a baby who develops normally. Two recent studies of the risk of major malformations, a national birth registry and a prospective single experience,² consisted mainly of carbamazepine (CBZ) or valproate (VPA) exposed pregnancies. Both suggested that first semester exposure to VPA monotherapy carried a higher risk of fetal malformation than exposure to CBZ monotherapy. There is an increased risk' for abnormalities in infants exposed in utero to phenobarbital, a drug that not long ago was the recommended drug for pregnant women with epilepsy (WINE).

In this and a future issue of *Neurology*, three birth registries are reported. Cunningham et al.⁴ report results from the lamotrigine (LTG) registry and Wyszynski et al.⁵ report results from VPA-exposed pregnancies. Both reports track major birth defects evident by ultrasound or inspection within the first few days of life. Artama et al.¹ report on the rate of malformations in offspring of WWE after exposure to several AEDs in monotherapy and polytherapy compared to offspring of untreated WWE.

Cunningham et al.⁴ report a 2.9% incidence of major defects in the infants of 414 WWE treated with LTG monotherapy. When LTG was used in polytherapy, there was a 12.5% incidence if it was used with VPA (88 exposures) and a 2.5% incidence with other AEDs (182 exposures). This multinational registry (12 years of observations) enrolled patients voluntarily by physician report, with postpartum physician information.

Wyszynski et al.⁵ report results from the North American AED Pregnancy Registry for VPA monotherapy, finding a 10.7% incidence of major malformations compared with a 2.9% incidence with other AED monotherapy use and a 2.6% incidence in a group of women without epilepsy. The study benefits from voluntary enrollment of WWE, by the use of

two predelivery and one postpartum interview; and from evaluation of medical records. Dysmorphologists made two independent evaluations of the abnormalities. The investigators controlled for maternal seizures and other confounding data. The relative risk of having an affected infant with VPA use was 7.3 compared with the general population rate. There was a trend for higher malformation occurrence with lower maternal education, smoking, and greater alcohol use.

Artama et al.⁵ describe a 9-year study comparing the rate of malformations in children of 1,411 WWE who took predominantly CBZ, oxcarbazepine (OXC), phenytoin, or VPA to the rate in children of WWE who did not take AEDs in the first trimester. The untreated population-based data are derived from registration for payment of AEDs in Finland (100% reimbursement). Malformations at birth were analyzed. Of 2,350 infants (939 exposed to AED; 1,411 not exposed), 3.4% had malformations (4.6% in the exposed cohort; 2.8% in the nonexposed cohort). Risk was greater in polytherapy (7.2%), with more than half of the malformations seen in children exposed to VPA polytherapy and a 10-fold risk at doses >1,500 mg/day. Whether in mono- or polytherapy, VPA use led to a fourfold risk for malformation. They also report the largest series thus far of OXC-exposed infants (99), noting only one malformation.

All three studies prospectively enrolled many WWE, but the numbers of pregnancies are too small to answer some important questions. Only Artama et al. report risks of specific malformations. There were no patterns of malformations with LTG or VPA, although neural tube defects may be more common in VPA-exposed fetuses than in the "other AED" group. The effect of the AED itself was not clarified by any of the studies. Pregnancy registries for women taking LTG or VPA monotherapy for indications other than epilepsy are not available. None of the studies clarified nutritional contributions, including folate

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supplementation. Does folate decrease the risk of malformations in WWE? Wyszynski et al.⁵ report 4 infants with spina bifida in the 106 VPA-exposed women who took folate, accounting for an incidence of 3.8%. Would this rate be higher without folate? Is folate needed throughout pregnancy or only preconception and through organogenesis?

In addition to structural defects, there are possible long-term cognitive effects of prenatal exposure to AEDs. Previous population-based prospective studies did not find that prenatal exposure to phenytoin (PHT) monotherapy^{7,9} or to CBZ monotherapy⁹ impaired intelligence. No sufficient prospective data on VPA monotherapy are available, but fetal VPA exposure may be harmful for verbal intelligence.⁹

Vinten et al.¹⁰ report the results of neuropsychological testing at ages 6 to 16 years in 249 children of WWE. Two-thirds of mothers had focal epilepsy, and one-third had idiopathic generalized epilepsy. One hundred twenty children were exposed to monotherapy: 52, CBZ; 41, VPA; 21, PHT; and 6, other. Forty-nine children were exposed to polytherapy, and 80 had no AED exposure. The mean verbal (but not performance or full-scale) IQ of those exposed to VPA monotherapy was lower than that of those exposed to other monotherapy regimens or those who had no exposure to AEDs.

The number of VPA monotherapy-exposed children in the study of Vinten et al.¹⁰ comprises the largest cognitive study to date. The most important potential confounding factor was controlled for elegantly and simply by measuring maternal intelligence. However, the results must be interpreted with caution. The retrospective design reduced the reliability of exposure data, and inclusion, based on the parents' willingness to participate, may create a bias in IQ results. It remains unexplained why only verbal intelligence was affected.

The Artama et al. study suggests that there may be a dose-response effect of valproate. None of the studies provides an explanation for the disturbance in fetal development. Without good animal models for human teratogenicity, the mechanism for the abnormalities remains unknown. Does VPA metabolism, P450 oxidation with a free radical intermediary, contribute to the teratogenicity? Or, might VPA's inhibition of metabolism of other drugs also contribute? Can we make a leap of faith and utilize drugs without such metabolic intermediates more confidently in pregnancy? LTG undergoes glucuronidation and not oxidation, yet some of the same malformations are seen. Future studies will be needed to address these important questions.

Although these studies do not provide absolute answers, they are important and needed to counsel WWE who contemplate pregnancy. The results from LTG monotherapy-exposed pregnancies are not alarming and may be somewhat reassuring; how

ever, as the authors note, the sample size is too small for definite conclusions. There are now data demonstrating structural and functional teratogenicity of VPA from several independent studies. However, because the choice of drug depends on the epilepsy syndrome, we cannot yet exclude the possibility that the results from prenatal VPA exposure may be in part associated with some maternal epilepsy characteristic that may predispose the child to malformations or developmental problems. The emerging data, however, should make the clinician consider an alternative to VPA therapy in WWE prior to conception.

Maintaining effective AED therapy during pregnancy is crucial. Maternal tonic-clonic status epilepticus may cause catastrophic damage to the fetal brain,¹² and even partial seizures may produce infant distress." Although new generation AEDs offer alternative treatment choices for many patients, many women with idiopathic generalized epilepsy continue to need VPA for seizure control." Data on the risk of malformations after prenatal exposure to newer AEDs are unfortunately almost completely lacking, other than for the present study on LTG.⁴

With this present knowledge, the risks for mother and child can be most effectively minimized by careful planning of AED therapy before pregnancy, by supplementing with folate, and by using monotherapy with the lowest effective dose of the AED that is most effective against seizures in that patient.

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