Antiepileptic drugs and breastfeeding
Do we tell women “no”?

Women with epilepsy (WWE) considering childbearing are usually advised to remain on antiepileptic drugs (AED) during pregnancy and throughout their reproductive years. Balancing the risk of seizures with the risk of AED exposure to the developing fetus has been actively investigated.1–3 Mounting evidence suggests that the effects of AEDs on the offspring can occur throughout pregnancy and possibly beyond with continued exposure.

Through international pregnancy registries, the rate of congenital malformations associated with first-trimester in utero AED exposure is one of the most widely studied outcomes.2 Results reflected in the American Academy of Neurology (AAN) guidelines show that valproic acid (VPA) use in the first trimester may contribute to the development of major congenital malformations.2 However, the effects of exposure to AEDs during brain development in the third trimester have been much less studied due to the need for sophisticated cognitive evaluation, behavioral testing, and prolonged follow-up. It is likely that in utero AED polytherapy and individual AEDs including VPA, phenobarbital, and phenytoin may lead to reduced cognition.2 The Neuropendvelopmental Effects of Antiepileptic Drugs (NEAD) study,4 a prospective observational study at 25 epilepsy centers in the United States and United Kingdom performed from 1999 to 2004, examined the possible adverse effects of 4 AEDs used as monotherapy (carbamazepine, lamotrigine, phenytoin, valproate) on cognition and behavior. At 3 years of age, children exposed in utero to VPA had an IQ 9 points lower than children exposed to lamotrigine.4

While in utero AED exposure cannot be avoided in most cases, AED exposure ex utero through breast milk is voluntary and could lead to further adverse cognitive and behavioral outcomes. While many AEDs including VPA, carbamazepine, phenobarbital, and phenytoin are transferred into the breast milk in small, perhaps clinically insignificant levels, some AEDs, such as levetiracetam and primidone, have a higher rate of transmission into breast milk. Unfortunately, there are few data on the neurodevelopmental effects of such AED exposure. The 2009 AAN Guidelines state that “There is no evidence to determine if indirect exposure to maternally ingested AEDs has symptomatic effects on the newborns of WWE,”3 but acknowledge that this is a source of continued anxiety for WWE.

In this issue of Neurology®, Meador et al.5 examined the cognitive outcomes of the breastfed offspring of WWE enrolled in the NEAD study. Of the 309 WWE enrolled in NEAD, 42% of children (n = 121) were breastfed. Mothers of breastfed children had higher IQ (104 vs 94), were older (31 vs 30 years of age), and more were taking folate (68% vs 53%) as compared to mothers not breastfeeding. The median time of breastfeeding was 6 months (range 3–24 months). There was no difference in the percent of WWE who breastfed in each AED group. After controlling for maternal IQ, mean IQ scores of offspring were 99 in the breastfed group and 98 in the non-breastfed group. Similar to the findings of the NEAD study,3 VPA was associated with lower IQ in a dose-dependent manner.

The transfer of medications into breast milk is difficult to study due to lack of standardization in obtaining breast milk and to other factors, including how frequently and how much a child is breastfed, the timing of collection (relative to feeding, drug dosing), and measuring medication in the milk itself or in the child. Foremilk and hindmilk have different protein, fat, and carbohydrate proportions, which can affect medication binding and secretion. New mothers are also presented with many challenges, including the child’s needs, sleep deprivation, and personal medical needs and emotional state, all of which make obtaining an ideal sample challenging. Finally, requesting that a mother donate milk or get a blood sample from a well child can be an emotionally and logistically insurmountable task. Drugs with higher protein binding (like VPA) have less excretion into...
the milk as compared to other AEDs like carba-
zaepine or lamotrigine. AED metabolism in the
newborn or infant may be different from in the
adult; few studies have examined the concentra-
tions of AEDs in children being breastfed by
WWE taking AEDs.

The study by Meador et al. is therefore important
due to the large numbers of WWE who gave breast
milk, the detailed follow-up of their children, and
the extensive cognitive information and testing. This
study provides the most information thus far as a
basis to counsel WWE. Breastfeeding has positive
emotional and psychological effects on the mother
and child and beneficial effects through decreased
risks for heart disease, diabetes, and obesity in the
child; and a decreased risk of breast and ovarian can-
cer in the nursing mother. There are several limita-
tions to this study. The numbers of subjects are
insufficient to detect differences among AEDs. Fur-
ther, there are no control groups for comparison,
such as WWE not taking AEDs or WWE taking
AEDs only during breastfeeding and not during ges-
tation. Despite these issues, this study offers reasur-
ance to WWE taking an AED that breastfeeding will
likely not significantly affect their child’s IQ.

However, there is still no definitive answer. There
is still a pressing need to gather more data on individual
AEDs in breast milk and their long-term effects,
so that neurologists, pediatricians, obstetricians,
and lactation consultants can better counsel reproductive
age WWE. This study also presents compelling rea-
sons why cognition and behavior in the offspring of
WWE should be more carefully monitored over a
longer period of development.

DISCLOSURE
Dr. Klein receives research support from the Epilepsy Foundation of
America, the American Epilepsy Society, and the American Headache
Society. Dr. Klein works in the same epilepsy division as Dr. Pennell.

REFERENCES
1. Harden CL, Hopp J, Ting TY, et al. Practice Parameter
update: management issues for women with epilepsy—
focus on pregnancy (an evidence-based review): obstetrical
complications and change in seizure frequency: Report of
the Quality Standards Subcommittee and Therapeutics and
Technology Subcommittee of the American Academy of
Neurology and American Epilepsy Society. Neurology
2009;73:126–132.
2. Harden CL, Meador KJ, Pennell PB, et al. Practice Param-
eter update: management issues for women with epilepsy—
focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: Report of the
Quality Standards Subcommittee and Therapeutics and
Technology Subcommittee of the American Academy of
Neurology and American Epilepsy Society. Neurology
2009;73:133–141.
3. Harden CL, Meador KJ, Pennell PB, et al. Practice Param-
eter update: management issues for women with epilepsy—
focus on pregnancy (an evidence-based review): vitamin K,
follic acid, blood levels, and breastfeeding: Report of the
Quality Standards Subcommittee and Therapeutics and
Technology Subcommittee of the American Academy of
Neurology and American Epilepsy Society. Neurology
2009;73:142–149.
4. Meador KJ, Baker GA, Browning N, et al. Cognitive func-
tion at 3 years of age after fetal exposure to antiepileptic
drugs. N Engl J Med 2009;360:1597–1605.
5. Meador KJ, Baker GA, Browning N, et al. Effects of
breastfeeding in children of women taking antiepileptic
drugs. Neurology 2010;75:1954–1960.
6. Ip S, Chung M, Raman G, et al. A summary of the Agency
for Healthcare Research and Quality’s evidence report on
breastfeeding in developed countries. Breastfeed Med
2009;4(suppl 1):S17–S30.