Current Literature
In Clinical Science

To Test Our Guess That Breast Is Best: Anticonvulsants and Breastfeeding

Effects of Breastfeeding in Children of Women Taking Antiepileptic Drugs.

Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW. *Neurology* 2010;75:1954–1960.

BACKGROUND: Breastfeeding is known to have beneficial effects, but there is concern that breastfeeding during antiepileptic drug (AED) therapy may be harmful to cognitive development. Animal and human studies have demonstrated that some AEDs can adversely affect the immature brain. However, no investigation has examined effects of breastfeeding during AED therapy on subsequent cognitive abilities in children. METHODS: The Neurodevelopmental Effects of Antiepileptic Drugs Study is an ongoing prospective multicenter observational investigation of long-term effects of in utero AED exposure on cognition. Between 1999 and 2004, we enrolled pregnant women with epilepsy who were taking a single AED (carbamazepine, lamotrigine, phenytoin, or valproate). We recently reported on differential AED effects on age 3 year cognitive outcomes. In this report, we focus on the effects of breastfeeding during AED therapy on age 3 cognitive outcomes in 199 children. RESULTS: A total of 42% of children were breastfed. IQs for breastfed children did not differ from nonbreastfed children for all AEDs combined and for each of the 4 individual AED groups. Mean adjusted IQ scores (95% confidence intervals) across all AEDs were breastfed = 99 (96-103) and nonbreastfed = 98 (95-101). Power was 95% to detect a half SD IQ effect in the combined AED analysis, but was inadequate within groups. CONCLUSIONS: This preliminary analysis fails to demonstrate deleterious effects of breastfeeding during AED therapy on cognitive outcomes in children previously exposed in utero. However, caution is advised due to study limitations. Additional research is needed to confirm this observation and extend investigations to other AEDs and polytherapy.

Commentary

Breastfeeding exists at a complex cultural crossroads in American society. The widespread use of infant formula for many decades left breastfeeding sorely underutilized and even eroded the very skill set itself, leaving subsequent generations of American women with inadequate resources to attempt it, even when motivated to do so. That motivation came from the steady stream of research articles establishing numerous health benefits from breastfeeding accruing to both child and mother, resulting in an aggressive push by both health authorities and grassroots advocates to increase breastfeeding rates. This, in turn, has spawned an occasional backlash, in part from harried mothers, unable or unwilling, who felt criticized for failing to meet this new maternal standard (1), and in part from prudish bystanders and managers of public spaces (2).

Mixing drugs with the milk produces additional cross-currents. Many educated mothers who would typically be interested in a "natural" or "healthy" lifestyle might be expected to be very favorably inclined to breastfeed. But if the mother in question has epilepsy, she is very likely under treatment with an antiepileptic drug (AED), and exposing one's baby to drugs is emphatically not "natural." Given the forced choice between exposing a newborn to an artificial food source or a CNS-active drug, breastfeeding is generally considered "elective" in the epilepsy population, and conservative obstetricians, pediatricians, and neurologists may counsel against it. Up to this point, the extant literature has been of little help in resolving this dilemma; the 2009 joint American Academy of Neurology/American Epilepsy Society (AAN/AES) practice parameter (3) noted only that the older AEDs (with the notable exception of primidone) may penetrate into breast milk less than many of the newer AEDs, but the clinical utility of this observation is mitigated by evidence that circulating levels in the newborn may be much lower than those in ingested breast milk (4), and by the fact that there is no clear standard for what AED level in a newborn can be considered "significant." This practitioner has generally taken the opposite tack, encouraging breastfeeding on the (admittedly speculative) reasoning that any harms from modest AED exposure are likely outweighed by the manifold established benefits of breastfeeding.

But a test is a better than a guess, so we can be grateful for the efforts of the NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study investigators for shining some light

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on this challenging issue. NEAD is a landmark project that has followed children born to mothers with epilepsy to the age of 3 years (and beyond) with the primary goal of elucidating cognitive effects from fetal AED exposure. The main paper from this study was published in 2009 (5), and the existence of this cohort has allowed the investigators to perform a follow-up analysis predicated upon the "natural experiment" of whether AED-treated mothers chose to breastfeed (42% of them did) or not.

In concept, the study was simple: the children's cognitive exam scores at the age of 3 years were compared among breastfed and non-breastfed groups for each of the four AEDs studied: phenytoin (PHT), carbamazepine (CBZ), valproate (VPA), and lamotrigine (LTG). In practice this was made highly complex by the nonrandomized nature of the study, necessitating statistical control for a large number of variables as well as the use of propensity scoring, a common method to account for the individualization of treatment (and used in this case to account for factors correlated with the choice to breastfeed). One noteworthy weakness of the study was that 25% of the children did not have cognitive evaluation at age 3; this considerable hunk of missing data had to be imputed from the children's last scores obtained at age 2.

The results were, for the most part, clear enough: no significant differences were seen between cognitive scores in breastfed children and those in non-breastfed children for any of the four AEDs. Having the cohort divided into eight segments necessarily resulted in small sample sizes (*n* ranged from 11 to 36), which is another major limitation of the study; but this seems to have been largely a nonissue, as the two groups of LTG-exposed children had *identical* scores, while the breastfed children in the CBZ and VPA groups had adjusted scores that were several points *higher*. Thus, it is difficult to argue that larger samples might reveal an important negative effect from breastfeeding for these three drugs.

For PHT, this issue is less clear-cut. Scores in the breastfed and non-breastfed PHT groups were 91 and 98, respectively. This was not significant, with the confidence intervals substantially overlapping; but the difference of seven points between the two groups would be clinically meaningful if true. Investigators in training are routinely lectured about the concept of "statistically significant but clinically meaningless," but much less is said about the converse circumstance—clinically meaningful but not significant—even though it may be of great importance in some cases. With regard to the present study, no claim should be made that breastfeeding was problematic in the PHT children, as the difference was not significant. But given the size of the difference, it is also problematic to aver that there is *no* difference—there might well be a clinically important difference, which did not yield statistical significance because of inadequate power.

The latter ambiguity notwithstanding, this paper helps fill an important void in the epilepsy literature, and, in this commentator's view, provides fairly strong evidence that we should encourage breastfeeding by mothers taking CBZ, LTG, or VPA. Although there are certainly limitations to the study, including the sample sizes and the lack of standardization of breast milk exposure (as mentioned in the incongruously titled editorial [6]), it is also true that there is unlikely to be a study performed with significantly better methodology owing to practical and ethical considerations. Future studies should employ similar methods to explore the effects of other AEDs, particularly those such as levetiracetam and oxcarbazepine, which show some early promise of low teratogenicity and thus may be used more in pregnant women going forward. We also clearly need to revisit the issue of PHT's breastfeeding effects, ideally with a larger sample size. All future studies of long-term cognitive effects in AED-exposed infants would be wise to follow the example of NEAD and collect breastfeeding data in the process; it's a great example of milking a study for maximum benefit.

by Scott Mintzer, MD

References

1. Rosin H. The case against breast-feeding. *Atlantic Magazine*. April 2009. http://www.theatlantic.com/magazine/archive/2009/04/the-case-against-breast-feeding/7311. Accessed April 4, 2011.
2. Harmon A. 'Lactivists' taking their cause, and their babies, to the streets. *The New York Times*. June 7, 2005. http://www.nytimes.com/2005/06/07/nyregion/07nurse.html. Accessed April 4, 2011.
3. Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, Hopp J, Ting TY, Hauser WA, Thurman D. Management issues for women with epilepsy—Focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding. *Epilepsia* 2009;50:1247–1255.
4. Tomson T, Palm R, Källén K, Ben-Menachem E, Söderfeldt B, Danielsson B, Johansson R, Luef G, Ohman I. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007;48:1111–1116.
5. Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med* 2009;360:1597–1605.
6. Klein A. Antiepileptic drugs and breastfeeding: Do we tell women "no"? *Neurology* 2010;75:1948–1949.

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