DRUGS, PREGNANCY, AND LACTATION

AEDs and Breastfeeding

Pregnant women with epilepsy have long been the focus of investigations regarding the safety of anticonvulsant agents for the developing fetus. Prenatal exposure to selected antiseizure medications in monotherapy and polytherapy has been linked to increased risks for specific congenital malformations. More recently, dose-related deficits in cognitive performance have been demonstrated with prenatal exposure to valproate.

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However, to date, little information has been available on the risks or safety of postnatal exposure to antiseizure medications via breast milk, specifically with respect to the potential impact on infant brain development. While it is typically necessary to continue treatment for a seizure disorder during pregnancy, the choice to breastfeed while taking antiseizure medication is considered voluntary. Given the multiple benefits of breastfeeding, the lack of compelling data on the safety of these medications during lactation creates a decision-making dilemma for women with seizure disorders and their health care providers.

A recently published study has shed some welcome light on this topic. Using data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, an ongoing, multicenter, prospective observational study in the United States and United Kingdom, the authors compared results of standard neurodevelopmental evaluations on 199 3-year-old children whose mothers had taken one of four antiepileptic drugs (AEDs) as monotherapy throughout and after pregnancy; less than half had been breastfed. A total of 58 children were prenatally exposed to carbamazepine, 66 to lamotrigine, 40 to phenytoin, and 35 to valproate. Among those, 26, 30, 17, and 11 children, respectively, continued to be exposed via breast milk for a period of time ranging from 3 to 24 months after birth.

Investigative staff, who were blinded to maternal/infant medication exposure status, measured cognitive outcomes in the study children using a standardized testing protocol conducted between 36 and 45 months of age.

Other important predictors of child performance, such as maternal IQ, maternal age, gestational age of the child at delivery, and preconception use of folate supplements, were taken into account in the analysis.

The authors, Dr. Kimford Meador of the department of neurology, Emory University, Atlanta, and his associates, reported no significant differences in mean child IQ across all medication categories for breastfed vs. nonbreastfed children. In addition, there were no significant differences in mean IQ scores within each of the four medication groups, although the numbers were small – particularly for those exposed to phenytoin and to valproate. As expected, adjusted mean IQ scores were lowest for the valproate-treated group, but were similar in breastfed and nonbreastfed children in that subset (Neurology 2010;75:1954-60) The study was funded by the U.S. National Institutes of Health/National Institute of Neurological Disorders and Stroke, and the U.K. Epilepsy Research Foundation.

These data provide some reassurance regarding mothers who are breastfeeding while being treated with one of the four medications – and the data are consistent with the concept that the dose being delivered to the infant or toddler via breast milk is limited relative to the dose available to the fetus in utero (Neurology 2010;75:e90-2).However, this study did not address several additional and important questions, including cognitive performance in infants and children who are breastfed by mothers who take any of the other AEDs, who are treated with polytherapy, or who take these medications for psychiatric or pain indications.

Mothers who are taking AEDs while breastfeeding, including the four included in the NEAD study, should continue to monitor their breastfed infants for adverse effects. Further follow-up on this cohort when the children reach school-age is warranted, and replication of the findings of this study in a larger sample size for specific medications, especially valproate, is needed.

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Obstetric History May Modify 17P's Effectiveness

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE SOCIETY FOR MATERNAL-FETAL MEDICINE

SAN FRANCISCO – Obstetric history may influence how much benefit pregnant women obtain from 17 alpha-hydroxyprogesterone caproate that is taken to prevent a recurrence of preterm delivery, according to results of a retrospective study.

All of the 7,319 pregnant women in the retrospective study were receiving 17 alpha-hydroxyprogesterone caproate (17P) because they had experienced at least one spontaneous preterm delivery (SPTD).

The group who had just a single SPTD was 17% less likely to have a recurrence if they had also experienced a prior term birth. There was a trend toward a benefit of a prior term birth only in the group who had had multiple SPTDs.

These findings raise the possibility that a prior term birth may modify the effectiveness of 17P, according to Dr. John R. Barton.

Still, "current information would suggest that 17P be offered to all women with a history of prior SPTD in a current singleton pregnancy, even if they have experienced a term gestation, especially now with the Food and Drug Administration's approval of 17P," he said at the meeting. The FDA said that it had approved 17P for the prevention of recurrent preterm birth in women with singleton pregnancies.

Investigators have noted a lack of direct data on the benefit of 17P in women with a prior term birth followed by SPTD, Dr. Barton observed. Additionally, some have expressed concern that this treatment may increase fetal loss.

He and his colleagues studied women with a singleton pregnancy who received weekly 250-mg intramuscular injections of 17P through a home administration program because of previous SPTD. Treatment began before 25 weeks' gestation and continued until 36 completed weeks or preterm delivery.

About 70% of the women had previously experienced just one SPTD, while the other 30% had experienced more than one, reported Dr. Barton, who is director of maternal-fetal medicine at Central Baptist Hospital in Lexington, Ky.

In the group who had just one SPTD, women with a prior term birth were significantly less likely than those without a prior term birth to have a recurrent SPTD before 37 weeks' gestation (odds ratio, 0.83), and also before 35 weeks (OR, 0.73) and before 32 weeks (OR, 0.74).

In a multivariate logistic regression analysis, a prior term birth still significantly protected against recurrent SPTD before 37 weeks (OR, 0.83; $P = .01$).

In the group who had more than one SPTD, women with a prior term birth were significantly less likely to have a recurrent SPTD before 37 weeks' gestation (OR, 0.79) but not before 35 or 32 weeks. And in a multivariate logistic regression analysis, there was a trend toward a lower risk of recurrent SPTD only before 37 weeks (OR, 0.83; $P = .06$).

Comparing results across singleton progestin studies, Dr. Barton noted that the rate of fetal death in the study cohort was just 0.37%, or much lower than the 1.3% observed in the placebo arms of two randomized trials (N. Engl. J. Med. 2003;348:2379-85; Ultrasound Obstet. Gynecol. 2007;30:687-96).

Moreover, those two trials were much smaller. Therefore, "I think we can conclude that our stillbirth rate was not increased above those in the placebo cohorts."

The study had its limitations, acknowledged Dr. Barton. It was retrospective, did not have data on cervical length, and lacked a control group not given 17P.

But there also were some noteworthy strengths. "This is the largest cohort of women with a prior SPTD evaluating 17P therapy in a community setting," he elaborated.

"It's also the first to evaluate the impact of a prior term delivery as a modifier of the risk of recurrent SPTD at less than 37, less than 35, and less than 32 weeks' gestation," Dr. Barton said. ■

VITALS

Major Finding: A prior term birth was independently protective among women who had just one previous spontaneous preterm delivery (OR, 0.83), but not among those who had more than one.

Data Source: Retrospective study of 7,319 women with a singleton pregnancy who received 17 alpha-hydroxyprogesterone caproate because they had previously experienced spontaneous preterm delivery.

Disclosures: Dr. Barton reported receiving support from Alere San Diego Inc. for preeclampsia research.