What Is My IQ: Cognitive Outcomes in Children With Fetal Exposure to Newer Anti-Seizure Medications

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Cognitive Outcomes at Age 3 Years in Children With Fetal Exposure to Antiseizure Medications (MONEAD Study) in the USA: A Prospective, Observational Cohort Study

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Background: The neurodevelopmental effects of fetal exposure to most antiseizure medications are unclear. We aimed to investigate the effects of fetal exposure to commonly used antiseizure medications on neuropsychological outcomes at age 3 years. Methods: The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is a prospective, observational, multicenter cohort study at 20 specialty epilepsy centers in the USA. We have investigated pregnancy outcomes in women (aged 14-45 years) with and without epilepsy who were enrolled during pregnancy ($\leq$20 weeks' gestational age), and their children. The primary outcome for children at age 3 years was a blindly assessed Verbal Index score, which was calculated by averaging scores on the Naming Vocabulary and Verbal Comprehension subtests of Differential Ability Scales-II, Expressive Communication and Auditory Comprehension subscales of Preschool Language Scale-5, and Peabody Picture Vocabulary Test-4. Children of women with and without epilepsy were compared, and the associations of medication exposures to outcomes in exposed children were assessed. The MONEAD study is registered with Clinical-Trials.gov, NCT0730170, and is ongoing. Findings: Between Dec 19, 2012, and Jan 13, 2016, 456 pregnant women (351 with epilepsy and 105 without epilepsy) were enrolled into the study. 345 children were born to women with epilepsy and 106 children were born to women without epilepsy. Verbal Index scores at age 3 years did not differ for children of women with epilepsy (n = 284; adjusted least-square mean 102.7, 95% CI 101.4 to 103.9) versus those without epilepsy (n = 87; 102.3, 99.8 to 104.7). Significant risk factors for reduced Verbal Index scores included maternal intelligence quotient, maternal education, post-birth anxiety, gestational age at enrolment, child's sex, and child's ethnicity. For Verbal Index scores, antiseizure medication exposure effects were not seen for maximum third trimester blood concentrations (n = 258; adjusted parameter estimate −2.9, 95% CI −6.7 to 1·0). However, in secondary analyses, exposure-dependent effects were present on multiple cognitive measures, which varied by medication. Interpretation: We found no difference in neurodevelopmental outcomes between children with fetal exposure to newer antiseizure medications compared with unexposed children. However, some exposure-dependent antiseizure medication effects were seen in secondary analyses. The adverse effects of maternal post-birth anxiety emphasize the importance of screening mothers during pregnancy and postpartum and implementing interventions. Additional studies are needed to clarify the exposure-dependent effects.

Commentary

Focus on the developmental and cognitive outcomes of an unborn child often drives treatment decisions in women with epilepsy (WWE). The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study investigated cognitive outcomes in children with fetal exposure to anti-seizure medications (ASMs) commonly prescribed between 1999 and 2004 in the United States and United Kingdom. The results demonstrated that impaired cognitive function was reported in children who had fetal exposure to valproate compared with 3 other anti-seizure monotherapies (ie, carbamazepine, lamotrigine, and phenytoin).[1,2] As a result, the US Food and Drug Administration put forth a warning for valproate use in pregnancy.[3,4] Since that time, patterns of prescribing ASM have changed; however, the risks associated with many of the newer ASMs remain unclear, especially for those related to teratogenic effects.[5]

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study was formulated to investigate pregnancy outcomes in women with and without

epilepsy, and the effects of ASMs on the exposed children. This 2023 study focused on the cognitive outcomes at age 3 years in children with fetal exposure to ASMs commonly used in pregnancy in the United States during 2012 to 2016.[6] It was a prospective observational cohort study, with the primary neurodevelopmental aim of comparing outcomes in children of WWE versus children of women without epilepsy (WWoE) to investigate if there was an exposure-dependent relationship between fetal exposure to ASMs and cognitive outcomes in children of WWE. The study enrolled 456 pregnant women, 351 with epilepsy and 105 without epilepsy, with 345 children born to WWE and 106 children born to WWoE. Verbal Index scores, calculated across multiple standardized vocabulary and verbal comprehension subtests, were assessed in 284 children of WWE and 87 children of WWoE. For children of WWE, the third trimester ASM regimen was analyzed, showing monotherapy for 210 (74%), polytherapy for 63 (22%), no ASMs throughout pregnancy for 10 (4%), and no third trimester exposure due to delivery in the second trimester for one. Of all 210 participants receiving monotherapy, the most common ASMs were lamotrigine (90 [43%]) and levetiracetam (74 [35%]). Additional monotherapies in at least 1% of mothers were oxcarbazepine (14 [7%]), carbamazepine (12 [6%]), zonisamide (11 [5%]), and topiramate (3 [1%]). The most common ASM polytherapy combination was lamotrigine with levetiracetam (26 [41%] of 63 polytherapies). Next, the relationship between ASM blood concentrations in the third trimester and the Verbal Index scores was analyzed, which included 258 children of WWE. No significant differences were seen in the Verbal Index scores between children of WWE versus WWoE. Significant factors in the full model included maternal IQ, education level, post-birth maternal anxiety, gestational age at enrollment, and child's sex and ethnicity. Analyses of 14 cognitive outcome measures comparing children of women with and without epilepsy were not statistically significant. Notably, measures of maternal depression, anxiety, and perceived stress showed an inverse relation to Verbal Index scores in unadjusted analyses, and adverse effects were seen for maternal depression and anxiety in adjusted models. While these findings did not differ for children of WWE versus WWoE, WWE had more symptoms of anxiety and depression in the post-birth period. Lastly, this study also investigated blood concentrations of ASMs in children of WWE who were breastfeed and demonstrated that blood concentrations of ASMs were generally low in these breastfeed children.

In summary, the findings of this study demonstrated that cognitive outcomes in children aged 3 years did not differ if their mother had epilepsy and was taking ASMs versus if their mother did not have epilepsy. Better verbal abilities were significantly associated with higher maternal IQ and education, less maternal post-birth anxiety, child being of female sex or of non-Hispanic or non-Latino ethnicity, and slightly fewer weeks of gestational age at enrollment. Post-birth anxiety in all mothers adversely affected child cognitive outcomes regardless of which group they were in. While WWE had more symptoms of anxiety and depression, this did not lead to differences in cognitive outcomes in their children. There was no association of Verbal Index scores with blood concentrations of ASMs in the third trimester across all categories and types of these drugs. Secondary analyses revealed negative effects on one measure on the Peabody Picture Vocabulary test-4 cross all ASMs, and for levetiracetam, on 5 of the 14 cognitive measures. Worse cognitive performance was associated with higher doses in the third trimester across all ASMs for 5 of the 14 cognitive measures, and exposure-dependent relationships were more apparent with levetiracetam. That said, children exposed to levetiracetam did not differ overall on cognitive outcomes from children of WWoE and thus, levetiracetam can be used safely in women of childbearing potential. These secondary analyses need to be interpreted with caution due to multiple comparisons and need replication to determine significance. Nevertheless, these findings support our common practice of avoidance of polypharmacy and higher dosing of ASMs in WWE to prevent exposure-dependent associations. In addition, the fact that blood concentrations of ASMs were generally low in breastfeed children, in combination with the known benefits of breastfeeding,[7] provides further evidence to support encouragement of WWE to breastfeed if that is something they desire.

Limitations of this study include that the authors could not randomly assign ASMs among the subjects due to the ethical and practical issues of investigations of pregnant WWE, which thus could introduce selection bias. In addition, neuropsychological assessments at age 3 years might not detect associations that may be seen at older ages. Lastly, while lamotrigine and levetiracetam are 2 of the most commonly prescribed ASMs in WWE of childbearing age,[8] the sample sizes for many of the other ASMs were small, preventing clear individual assessments of other drugs.

This publication demonstrates the importance of balancing the conversation regarding the benefits of maintaining individual target ASM blood concentrations to lower the risk of seizures with the conversation about unnecessary medication over-exposure to the developing fetus, highlighting the importance of investigating the relationships between ASMs and cognitive outcomes. Emphasis should be placed on the consideration of dosing levels of ASMs during pregnancy, given that the full teratogenic effects of most ASMs continue to remain unknown.[5] That said, this study showed that there was no difference in cognitive outcomes in children aged 3 years related to whether their mother had epilepsy or not. This study also highlighted the crucial broad effect of maternal anxiety and mood on the neurodevelopment in all children and reinforced the necessity for routine screenings and intervention in the postpartem period for all woman. It is important to note that if post-birth anxiety is identified, targeted interventions could be implemented, which in turn could possibly improve cognitive outcomes across all children. Lastly, the teratogenic effects of ASMs remain an important area for

future research, along with further exploration into the genotypic risk factors for ASM teratogenicity. Further studies could be used to help best educate and plan for safe and healthy pregnancies for our patients.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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