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Exploring the Cognitive Outcomes of Children Prenatally Exposed to Antiseizure Medications: Mind the Lab

Two-Year-Old Cognitive Outcomes in Children of Pregnant Women With Epilepsy in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Study

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Importance: The neurodevelopmental risks of fetal exposure are uncertain for many antiseizure medications (ASMs). Objective: To compare children at 2 years of age who were born to women with epilepsy (WWE) vs healthy women and assess the association of maximum ASM exposure in the third trimester and subsequent cognitive abilities among children of WWE. Design, setting, and participants: The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study is a prospective, observational, multicenter investigation of pregnancy outcomes that enrolled women from December 19, 2012, to January 13, 2016, at 20 US epilepsy centers. Children are followed up from birth to 6 years of age, with assessment at 2 years of age for this study. Of 1123 pregnant women assessed, 456 were enrolled, 426 did not meet criteria, and 241 chose not to participate. Data were analyzed from February 20 to December 4, 2020. Main outcomes and measures: Language domain score according to the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), which incorporates 5 domain scores (language, motor, cognitive, social-emotional, and general adaptive), and association between BSID-III language domain and ASM blood levels in the third trimester in children of WWE. Analyses were adjusted for multiple potential confounding factors, and measures of ASM exposure were assessed. Results: The BSID-III assessments were analyzed in 292 children of WWE (median age, 2.1 [range, 1.9–2.5] years; 155 female [53.1%] and 137 male [46.9%]) and 90 children of healthy women (median age, 2.1 [range, 2.0–2.4] years; 43 female [47.8%] and 47 male [52.2%]). No differences were found between groups on the primary outcome of language domain (−.5; 95% CI, −4.1 to 3.2). None of the other 4 BSID-III domains differed between children of WWE vs healthy women. Most WWE were taking lamotrigine and/or levetiracetam. Exposure to ASMs in children of WWE showed no association with the language domain. However, secondary analyses revealed that higher maximum observed ASM levels in the third trimester were associated with lower BSID-III scores for the motor domain (−5.6; 95% CI, −10.7 to −.5), and higher maximum ASM doses in the third trimester were associated with lower scores in the general adaptive domain (−1.4; 95% CI, −2.8 to −.05). Conclusions and relevance: Outcomes of children at 2 years of age did not differ between children of WWE taking ASMs and children of healthy women.

Commentary

Less than a decade ago, the FDA's boxed warning for the fetal risk of valproate highlighted neural tube defects and other major malformations.[1] This has changed in 2013, when "decreased IQ" was added to the warning, specifically citing the large cohort study published in the same year by the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group.[2] The NEAD Study demonstrated a dose-dependent, deleterious effect of *in utero* exposure to valproate monotherapy on IQ scores at infancy and at school age. At age 6, the adjusted IQ of valproate-exposed children was reduced by 7–11 points vs children exposed to lamotrigine, carbamazepine, or phenytoin (the latter being comparable to values expected for the general population). In addition, children whose mothers were treated with valproate or lamotrigine had lower verbal vs nonverbal skills. When translating those findings to daily practice, one may consider that the exposure–response relationships relied on doses averaged for the whole pregnancy, likely underestimating the exposure to lamotrigine during the third trimester: the mean daily lamotrigine dose was 457 mg, but the third-trimester doses associated with the reported outcomes could have been much higher, as practiced at times during late-pregnancy (usually guided by lamotrigine plasma levels).

The outcomes of the NEAD and other studies and data from pregnancy registries, combined with tightened regulation on valproate use in women of childbearing potential, had a substantial impact on prescribing of antiseizure medications (ASMs). Valproate was no longer a drug of choice for women who are or may become pregnant, while the use of levetiracetam surged.[3] Other

questions remained to be answered though and new data were required to reflect the change in ASM use, driven in part by findings from the NEAD Study itself.

The Maternal and Neurodevelopmental Outcomes of in Utero Antiepileptic Drug Exposure (MONEAD) is a continuation of the NEAD Study, with a new cohort of pregnant women with epilepsy (WWE) and their children. Whereas the initial study focused primarily on the child's outcomes, MONEAD assesses maternal outcomes as well and includes a reference cohort of healthy women. The highlighted article[4] is the first report of the cognitive outcomes of the children participating in this study. The objectives here were to compare cognitive development at 2 years of age between children born to WWE and those born to healthy women and to explore the relationships between cognitive abilities and ASM levels in plasma. Assessment was based on the standardized Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) which incorporates 5 developmental domain scores. The language score was selected as the primary outcome because the investigators hypothesized that certain ASMs would be associated with impairment of verbal intellectual abilities, based on the above-mentioned findings from the NEAD Study.[2] For between-group comparisons, data from the ASM-exposed children were grouped, despite the heterogenicity in drug exposure. Exposure was defined for third trimester only and plasma ASM concentrations were a main variable. For that purpose, maximal plasma concentrations were normalized by the upper limit of the suggested therapeutic range. The data was adjusted for many potentially confounding factors.

No difference was found in the language or other domains between children exposed to ASMs and those born to healthy mothers, likely reflecting the shift to newer and safer ASMs. Breastfeeding and folate supplementation did not affect infants' intellectual development either, and breastfeeding may have even improved it. However, the investigators commented that the planned neuropsychological assessment at 6 years of age would be more predictive of adolescent and adult functioning.

Given the reassuring results of this study, some findings might be overlooked: ASM doses and maximal levels correlated with lower scores in domains other than language. More specifically, higher maximal levels of levetiracetam were associated with poorer motor development (−13.0; 95% CI, −22.1 to −4.0). That is, third-trimester maternal levetiracetam level of 50 μg/mL vs 10 μg/mL (1.25 and .25 the maximal recommended level, respectively) would predict a difference of 13 points on a score that ranges between 46 and 154 points.[5] Similarly, levels of 35 μg/mL vs 15 μg/mL, both well within levetiracetam's therapeutic range, correlate to a decrement of 6.5 points. For the majority of exposed children these differences may not be clinically significant. However, the increased scatter of motor performance observed at higher levetiracetam concentrations suggests that outliers with greater deviations from expected trajectories should be considered.

Why is it important to monitor maternal ASM levels during gestation? First, pregnancy can increase the within- and between-subject pharmacokinetic variability. One extreme example is the bimodal change in lamotrigine's oral clearance as pregnancy advances, with 10-fold higher change in 77% of women as compared to the other 23%.[6] Hence, plasma ASM concentrations are a more sensitive parameter than the dose, and correlating the infant outcomes to ASM levels may enable more effective and safer dose adjustment during pregnancy, particularly for lamotrigine and levetiracetam. Second, many small molecules, including lamotrigine and levetiracetam, are expected to freely diffuse across the placenta. Therefore, for the majority of ASMs, it can be assumed that maternal plasma concentrations correlate with those in fetal blood. Third, maternal plasma levels may directly represent those at another relevant target, the placenta itself. For instance, in cultures of trophoblast cells, levetiracetam downregulated in a concentration-dependent manner the expression of transporters for compounds that affect the cognitive development of the fetus.[7] From a clinical point of view, some supposedly unexpected adverse fetal outcomes could potentially be prevented if exceptionally high ASM concentrations in maternal plasma are identified.

In this context, we do not know if "flatter is better", that is, whether the adverse cognitive outcomes of the offspring are related to maximal ASM concentrations or to the overall drug load. The former may indicate the maximal boundary of exposure and yet are a less robust parameter since they reflect a single time point along a period of approximately 3 months.

Despite the established roles of breastfeeding in the well-being of both infants and mothers, WWE are more reluctant to breastfeed than healthy women, particularly if they are being treated with lamotrigine.[8] Infant exposure to many drugs in breastmilk is < 10% the exposure of the fetus in utero,[9] but lamotrigine is indeed efficiently transferred from maternal plasma to breastmilk.[10] This highlights the importance of the breastfeeding safety data added by the MONEAD Study.

Limitations of the study include lack of randomization, intensive monitoring and selection of ASMs that do not necessarily reflect WWE in the general population, and small sample sizes for ASMs other than lamotrigine and levetiracetam. Hence, the identification of an adverse fetal outcome of levetiracetam reflects primarily sufficiently large cohort of levetiracetam-treated women and not necessarily the safety of other ASMs. The major strengths of the study are in its prospective design; the thorough, long-term data collection; and the use of plasma ASM levels and not only drug doses.

Unfortunately, drug labeling and the media tend to adopt alarming information but not findings that might encourage WWE to adhere to their treatment, even when data regarding safety is available. It is therefore our duty to convey reassuring data, when available, to the many WWE who worry about taking ASMs during pregnancy and breastfeeding as well as to our students and fellows. Overall, the results described here prodive such information, keeping in mind that they represent an interim analysis, and that the positive finding was in a domain that was not part of the primary planned outcome. Yet, they support the often-debated need for frequent monitoring of ASM

concentrations in maternal plasma before and during pregnancy and for obtaining plasma levels in studies that assess the outcome of prenatal ASM exposure.

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References

1. U.S. Food & Drug Administration. Drugs@FDA: FDA-approved drugs. https://www.accessdata.fda.gov/scripts/cder/daf/. https://www.accessdata.fda.gov/scripts/cder/daf/, Accessed August 29, 2021.
2. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol*. 2013;12:244-252.
3. Meador KJ, Pennell PB, May RC, et al. Changes in antiepileptic drug-prescribing patterns in pregnant women with epilepsy. *Epilepsy Behav*. 2018;84:10-14.
4. Meador KJ, Cohen MJ, Loring DW, et al. Two-year-old cognitive outcomes in children of pregnant women with epilepsy in the maternal outcomes and neurodevelopmental effects of antiepileptic drugs study. *JAMA Neurology*. 2021;78:927-936.
5. Albers CA, Grieve AJ. Test Review: Bayley, N. In: *Bayley scales of infant and toddler development*. 3rd ed. San Antonio, TX: Harcourt Assessment Journal of Psychoeducational Assessment; 2007:Vol. 25:180-190.
6. Polepally AR, Pennell PB, Brundage RC, et al. Model-based lamotrigine clearance changes during pregnancy: clinical implication. *Ann Clin Transl Neurol*. 2014;1:99-106.
7. Tetro N, Moushaev S, Shmuel M, Eyal S. Antiseizure medications and fetal nutrients: effects on choline transporters in a human placental cell line. *Epilepsia*. 2021;62:1451-1459.
8. Al-Faraj AO, Pandey S, Herlihy MM, Pang TD. Factors affecting breastfeeding in women with epilepsy. *Epilepsia*. 2021;62:2171-2179. DOI: 10.1111/epi.17003.
9. Verstegen RHJ, Anderson PO, Ito S. Infant drug exposure via breast milk. *Br J Clin Pharmacol*. 2020. Doi: 10.1111/bcp.14538.
10. National Library of Medicine (US). Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): Lamotrigine; 2006. [Updated 2021 Aug 16]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501268/#. Accessed August 27 2021.