



What Should We Do When the Kids Grow Up? Studying the Long-Term Cognitive Effects of In-Utero Anti-Seizure Medication Exposure

Enduring Language Deficits in Children of Women With Epilepsy and the Potential Role of Intrauterine Exposure to Antiepileptic Drugs

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Objective: Exposure to certain intrauterine antiepileptic drugs (AEDs) can negatively influence the language skills and intelligence of young children. It remains unanswered whether these deficits are transient or persist as children grow up. This study aims to evaluate the language function of children of women with epilepsy (CWE) aged 9 to 13 years in comparison with their peers, and its relationship with intrauterine AED exposure. **Methods:** We included 191 CWE in our study from the Kerala Registry of Epilepsy and Pregnancy. Children in the same age group ($n = 144$) and without maternal epilepsy or antenatal AED exposure served as controls. We used Clinical Examination for Language Function version IV to assess language in both groups. Relevant data related to maternal epilepsy and AED use were obtained from the registry records. **Results:** The average Core Language Scaled Score (CLSS) was significantly lower in CWE as compared to controls (83.19 vs 90.18, $P = .001$). Similarly, the mean scaled scores in other language parameters were also significantly lower in CWE. In the multivariate analysis, compared to control children, the average CLSS in CWE was 4.5 units lower (95% CI = -8.8 to -0.2 , $P = .04$) with AED monotherapy exposure and 7.3 units lower with exposure to AED polytherapy (95% CI = -13.8 to -0.8 , $P = .03$). Intrauterine exposure to phenobarbitone ($n = 61$) and valproate ($n = 55$) as either monotherapy or polytherapy showed a negative effect on CLSS in CWE as compared to control children. However, carbamazepine ($n = 75$) and phenytoin ($n = 37$) use was not associated with significant variation of CLSS. In head-to-head comparisons between AED monotherapies in CWE, phenobarbitone showed a negative effect on CLSS (-14.7 , 95% CI = -23.1 to -6.4 , $P = .001$) as compared to carbamazepine. **Significance:** Intrauterine exposure to phenobarbitone and valproate impairs language development in CWE, with effects persisting into the second decade.

Commentary

When I was pregnant, I was told that a medication was “safe” for me to take in pregnancy. The supporting information I was given did not meet my standards, the standards I hold for the evidence I routinely present to women with epilepsy (WWE) who are pregnant or planning pregnancy. This experience reminded me how epileptologists stand apart from most specialists in how much we know about the effects of the drugs we prescribe on children exposed in-utero.

Thanks largely to the international pregnancy registries, which began to enroll pregnant WWE in the late 1990s, our field has invaluable prospective data on the frequency of major congenital malformations (MCMs) in children exposed to anti-seizure medications (ASMs). Prospective parents, however, are

interested not only in the risk of malformations but also in how their child will perform in school and in the world after school. Fortunately, epilepsy researchers are making headway in this area too. Several of the epilepsy pregnancy registries have also published on the effects of ASM exposure on development and behavior in young children. Additionally, a few independent prospective studies have been dedicated to understanding the cognitive and behavioral effects of ASMs.¹⁻³ These studies have largely been concordant in describing the negative effects of in-utero valproic acid exposure on cognitive and behavioral development in young children. Whether other ASMs have more subtle effects of intellectual or behavioral development is still under investigation, and results for some drugs have differed across





studies. Furthermore, only a few studies have investigated the lasting effects of ASM exposure on cognition and school performance in children beyond grade school.^{4,5}

The Kerala Registry of Epilepsy and Pregnancy (KREP) in India is one of the epilepsy pregnancy registries that has given us important data about ASM effects on both MCM risk and cognitive development. The Kerala Registry of Epilepsy and Pregnancy was established in 1998. The registry recruits women at the preconception stage or in first trimester of pregnancy and follows their children through the age of 18. In the article that is the focus of this commentary, the authors report on the language scores of 191 children born to mothers with epilepsy (CWE) when the children were between the ages of 9 and 13.⁶ The control group in this study was a group of 144 children randomly selected from 2 schools in the regional school district. This study complements a similar study from KREP that focused on IQ scores of their cohort in the same age group.⁷ The prior study had a largely overlapping group of participants but there are small differences in the cohort size and medication exposures between the 2 studies.

The principal finding of the present study was that preteens born to WWE had poorer standardized language scores compared to their peers. The Core Language Scale Score (CLSS) was the evaluation used in this study. The average CLSS score in children born to mothers with epilepsy was lower than that in control children (83.2 vs 90.2, $P = .001$). Specifically, 32.4% of the CWE had CLSS scores that were at least one standard deviation below the mean of the control group. Polytherapy was associated with greater decreases in CLSS than monotherapy, but both types of exposure had a significant association with lower CLSS scores.

It is important to note that the majority (60.7%) of the mothers in this cohort were taking valproic acid or phenobarbital during pregnancy, thus the principal finding of lower language scores in CWE should not be generalized to all children born to mothers with epilepsy or to all ASM exposures. In multivariate analyses, lower CLSS scores were associated with exposure to either valproate (-7.75 , 95% CI: -13.3 to -2.2 , $P = .006$) or phenobarbital (-8.85 , 95% CI: -14.5 , -3.2 , $P = .002$). On the other hand, exposure to carbamazepine or phenytoin was not associated with a significant change in language scores compared to the control group. Also of interest, when CWE exposed to carbamazepine or phenytoin were compared to the other CWE in the cohort, their scores were significantly better. This is a valuable addition to existing literature as cognitive outcomes with carbamazepine and phenytoin have varied across studies.^{1-3,8,9} Another notable finding is that children with MCMs were more likely to have poorer language scores than other CWE (72.29 vs. 83.55, $P=0.019$).

The major strength of this study is the long-term prospective data on CWE. The authors note that of the eligible 334 participants from KREP that were eligible to participate, 57% responded and were included in the present study. Retention is key in this type of this study but also very difficult. Retaining

more than half the subjects for over 10 years requires great persistence. There is, of course, some risk that the parents not responding were less concerned about their children's abilities. The authors performed a sensitivity analysis that demonstrated no significant differences in maternal characteristics or drug exposures between the group that participated and those that were not included.

The assessors in this study were blinded to the subjects' exposure status, which is another strength of the study. The analysis did not control for parental IQ or language abilities, which are important predictors of a child's skills. Instead, it did control for maternal education, which was a significant variable in the multivariate analyses. Finally, the analysis did not control for folic acid usage. The authors share that 23% of the mothers with epilepsy were not taking folic acid during the first trimester of pregnancy and this info was not available for the cross-sectional control group. This is worth noting given the increasing awareness that periconception folic acid may play a role in language development in both in children born to WWE and in the general population.^{3,10}

With their two studies of pre-teen cognition and language scores, the investigators of KREP have shown us the importance of looking at the long-term effects of ASM exposure. They also illustrate one successful way to conduct this research. The landscape of ASM use in pregnant women is changing drastically. Newer ASMs such as lamotrigine and levetiracetam are more commonly prescribed to WWE of childbearing age while, in many countries, the use of phenobarbital, valproate, carbamazepine, and phenytoin in this population is declining. Although we have valuable data on how levetiracetam and lamotrigine affect early childhood development, we will need much more information on how exposure to these medications impacts children beyond grade school. Additionally, we have several new medications that have come to the market in the last decade, and, on these, we have nearly no meaningful data on the risk of structural or cognitive teratogenesis. Finally, we need to know whether children who do have learning and behavioral challenges related to ASM exposure benefit from educational interventions provided to other children. Thus, to stay ahead of the curve, we need to be forward-thinking in studying the children born to WWE as the founders of KREP and others have been in the past. This includes retaining connection with those families currently enrolled in prospective studies of early childhood development and designing careful cross-sectional studies of children with a history of in-utero ASM exposure.

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