Do My Children Have a Higher Risk of Epilepsy Because of My Epilepsy or Seizure Medications?

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A question frequently posed by expectant mothers with epilepsy is “Do my children have a higher risk of epilepsy because of my epilepsy or seizure medications?” and its significance cannot be overstated. While genetic factors likely play a significant role, several studies have indicated a higher risk of epilepsy in children born to mothers with epilepsy compared with those born to fathers with epilepsy, coining the term maternal effect.1-4 However, this maternal effect was not observed in a cohort of families with epilepsy.5 One plausible explanation is that this maternal effect might, in part, be attributed to prenatal exposure to antiseizure medications (ASMs). In vitro and animal studies have shown that certain ASMs are associated with anomalous fetal brain development. In addition, human studies suggest neurodevelopmental effects associated with prenatal exposure.

Despite these findings, population-based studies to assess outcomes associated with prenatal medications present numerous challenges. They necessitate meticulous consideration of confounding factors, including epilepsy diagnosis, lifestyle changes, and subsequent biased medication selection. Additionally, they require a substantial sample size and prolonged longitudinal follow-up, which come with limitations in terms of control and data availability.

This study by Dreier et al6 investigates the association of prenatal exposure to different ASMs with the subsequent risk of epilepsy in exposed children. A notable strength of this prospective, population-based cohort study is the substantial number of mother-child pairs it encompasses, with a total of 38,663 children born to mothers with epilepsy. Moreover, Dreier et al6 have conducted comparisons between exposed and unexposed siblings, as well as cohorts of children whose mothers were using the same ASM: 1 cohort with prenatal exposure to ASMs and 1 cohort with maternal discontinuation of ASM prior to pregnancy. Additionally, by limiting the study population to children born to mothers with active epilepsy, Dreier et al6 have made efforts to account for variations in maternal epilepsy types, further enhancing the study’s robustness and relevance. This unique approach provides valuable insights into the true contribution of prenatal exposure to ASMs in association with the development of epilepsy.

Dreier et al6 identified a 2-fold increase in the risk of epilepsy among children whose mothers used valproate, topiramate, and possibly clonazepam during pregnancy. However, it is noteworthy that this risk was not significant when comparing exposed children with their unexposed siblings or with children of mothers who discontinued these ASMs before conception. One might question whether the discontinuation of ASMs indicates improved seizure control or a difference in the type of epilepsy. As such, Dreier et al6 conducted a secondary analysis on a restricted sample of mothers with active epilepsy, and these associations persisted. To delve deeper into a potential association between heightened epilepsy occurrence and prenatal ASM exposure, Dreier et al6 conducted a dose-response analysis. They were able to demonstrate the well-established dose-dependent association of risk of autism spectrum disorders and major congenital malformations with valproate exposure, but this dose-response association was not observed in terms of the offspring’s risk of epilepsy. In contrast, no increased risks for developing epilepsy were found with prenatal exposure to lamotrigine, levetiracetam, carbamazepine, or oxcarbazepine.

Based on their findings, Dreier et al6 conclude that the positive association of prenatal exposure to valproate and other ASMs with the risk of epilepsy in children of mothers with epilepsy is likely not...
a direct association but rather confounded by the indication for using these medications. These results provide some reassurance for individuals using valproate during pregnancy.6

But do they? A close read reveals that, in the study by Dreier et al,6 siblings of children who were exposed to valproate exhibited higher rates of major malformations compared with children in the general population (6% vs 3%). This finding could again be attributed to genetic factors, but it raises the possibility that maternal valproate use, either during pregnancy or limited to preconception, may impact children both directly and through genetic, epigenetic, and environmental modifications and increase their developmental risks. Furthermore, if this is the case, it raises questions about the potential risks associated with paternal use of valproate. While it is worth noting that 2 prior studies from 2013 did not find evidence of increased risks to children with paternal use of ASMs,7,8 the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance is actively supporting an ongoing retrospective study to better assess the potential risks associated with paternal use of valproate.9

In summary, this study by Dreier et al6 brings us closer to understanding the full health implications of maternal ASM use. While providing reassurance that, when needed, prenatal valproate and other ASMs are unlikely to independently confer an added burden of epilepsy to children, it does raise the concern of a heightened risk of major congenital malformations not only in the child exposed to valproate, but also among presumed unexposed siblings. Dreier et al6 should be commended for using the comprehensive database of the Nordic registries to provide individuals who are pregnant or trying to become pregnant with a better chance at making balanced, evidence-informed decisions for themselves and their children.

ARTICLE INFORMATION
Published: February 26, 2024. doi:10.1001/jamanetworkopen.2023.56379
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Conflict of Interest Disclosures: Dr Voinescu reported receiving personal fees from Stony Brook University, Neurodiem, Harvard University, and Philippines League Against Epilepsy and grants from Epilepsy Foundation of New England, National Institutes of Health, Karger Fund, Doremus Fund, and Brigham and Women's Hospital Connors Center outside the submitted work. No other disclosures were reported.
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