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Teratogenicity and Antiseizure Medications

Comment on: Meador KJ. Teratogenicity.
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The first modern antiseizure medication, bromide, was discovered in the 1850s, but it was not until the 1960s that the teratogenic effects of antiseizure medications were disclosed in studies initiated after the thalidomide tragedy highlighted the potential teratogenic effects of medications. A variety of malformations have been related to antiseizure medications including cardiac malformations, orofacial clefts, skeletal, urologic, and neural tube defects. In 1982, the first specific malformation linked to a specific antiseizure medication (spina bifida for valproate) was reported,[1] but it would not be until the 21st century that risks of antiseizure medication including the relative differential risks of antiseizure medications would become clearer. The lack of knowledge at the end of the 20th century is evident by the American Academy of Neurology practice parameters published in 1998 on management issues for women with epilepsy. The conclusions noted strong scientific evidence for the teratogenic effects of antiseizure medications in animals but stated that information from human studies was less certain.[2] The guideline offered no advice on differential risks across antiseizure medications.

In this setting, Epilepsy Currents[3] highlighted an article published in the New England Journal of Medicine in 2001, which described an investigation by Holmes et al who screen a cohort of 128 049 children born at Boston area hospitals.[4] They found that infants with fetal exposure to monotherapy or polytherapy with antiseizure medications had an increased risk for major congenital malformations and other physical abnormalities. Their study confirmed observations in prior studies and provided improved estimates of the risk. Further, their study demonstrated that infants born to women with epilepsy who were not taking antiseizure medications during pregnancy were not at increased risk. Prior to this time, concern was raised that the genetics related to epilepsy itself in women with epilepsy or their seizures during pregnancy might contribute to the observed malformations separate from antiseizure medications. However, it appears that the genetics related to the teratogenic effects of antiseizure medications are largely separate from genetics related to their epilepsy.

In the subsequent 2 decades, we have expanded our knowledge of the teratogenic effects of antiseizure medications. The establishment of several antiseizure medication pregnancy registries began to reap benefits in the early 21st century. A striking and repeated finding has been that fetal valproate exposure poses a dose-dependent risk for malformations that exceeds other antiseizure medications.[5-8] Dose-dependent effects for malformations have also been found for a few other antiseizure medications.[7] Teratogens act in a dose-dependent manner, and this study suggests that even some of our apparently safer antiseizure medications in regard to malformations appear to have dose-dependent risks. Although the data for most antiseizure medications are inadequate, these findings raise the possibility that all antiseizure medications may exhibit dose-dependent teratogenic effects. Based on present data, differential anatomical teratogenic effects of fetal antiseizure medication exposures have been demonstrated with the highest risk for valproate, but there are also intermediate risks for phenobarbital and topiramate, and the lowest risks are seen for carbamazepine, lamotrigine, levetiracetam, and oxcarbazepine.[8-11] Data on the risks of anatomical teratogenicity for all other antiseizure medications are inadequate or absent. The risks for many polytherapies have been reported to be driven largely by valproate,[12] but information on the safety of most polytherapies is uncertain.

Not only can fetal exposure to antiseizure medications produce anatomical teratogenic structural anomalies but it can also result in behavioral teratogenicity with cognitive deficits and behavioral abnormalities. A prospective, observational, multicenter investigation found that children exposed in utero to valproate had lower IQ compared to carbamazepine, lamotrigine, or phenytoin.[13,14] Effects of fetal valproate exposure across multiple cognitive domains have also been found. Similar to malformations, the effects of valproate on cognition are dose-dependent. However, even at doses less than 800 mg/d there are adverse cognitive effects, so a safe dose of valproate is unclear.[15] In addition to cognitive deficits, fetal valproate

exposure has also been linked to an increased risk for autism and autism spectrum disorder.[16] Levetiracetam has also demonstrated less cognitive effects than valproate.[17] Data on the risks of behavorial teratogenicity for all other antiseizure medications are inadequate or absent.

The prospective, observational, multicenter investigation mention above also found that the use periconceptional folate by women with epilepsy taking antiseizure medications was related to higher IQ in their children.[14] Consistent with this finding, population-based, prospective Norwegian studies have shown that periconceptional folate supplementation appears to reduce language delay and autistic traits in children exposed in utero to antiseizure medications.[18,19] Since most pregnancies are not planned, encouraging folate supplementation in women of childbearing potential taking antiseizure medications is important.

Despite the known positive effects of breastfeeding in the general population, concerns were raised for potential adverse neurodevelopmental effects on the immature brain of antiseizure medication exposure from breastfeeding when their mothers are taking antiseizure medications. However, no adverse cognitive effects have been seen at age 3 years old in 2 studies, and even positive cognitive effects were seen at age 6 years old in one of these cohorts.[20,21]

The expansion of our knowledge on the teratogenicity of antiseizure medications over the last 2 decades has changed guidelines and labeling, altered the management of women with epilepsy, and reduced malformations. However, there is much that remains unknown on how to direct the care of women with epilepsy during childbearing age. The anatomical and behavioral teratogenic risks for most antiseizure medications remain inadequate or are completely unknown. Beyond the few antiseizure medications which appear to be relatively safe, the physician has no evidence to guide selection of antiseizure medications in women of childbearing potential. Further, the mechanisms underlying both anatomical and behavioral teratogenic effects of antiseizure medications are poorly delineated. Without this knowledge, we cannot fully understand the risks much less design approaches to mitigate adverse effects. For example, teratogens act on a susceptible genotype, but the genetic risks for teratogenic deficits induced by fetal antiseizure medication exposures are unknown. There are probably multiple mechanisms, and they likely differ for anatomical and behavioral teratogenicity.

We need to expand our knowledge, so that our management of women with epilepsy can continue to evolve. Although the pace of progress in the last 2 decades exceeds the prior 150 years, it remains painfully slow for those women requiring antiseizure medications who want to have healthy children, and for their physicians trying to maximize pregnancy outcomes and avoid the lifelong consequences of malformations and diminished developmental outcomes in the children of women with epilepsy. Recommendations for new approaches to expediate obtaining the necessary knowledge and avoid exposing more children needlessly include a national reporting system for congenital malformations, ongoing routine meta-analyses of cohort studies to detect teratogenic signals earlier, monitoring of antiseizure medication (AED) prescription practices and folate use in women to determine whether additional educational efforts are needed, routine preclinical testing of all new AEDs for neurodevelopmental effects, and improved basic and clinical research funding to fully delineate risks and the underlying mechanisms of antiseizure medication-induced teratogenesis.[10]

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