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Risks of In Utero Exposure to Valproate

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Antiepileptic medications are among the most commonly prescribed teratogenic drugs among women of childbearing potential. However, determining the exact number of women of childbearing age exposed to antiepileptic medications is difficult. One estimate, based on data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, suggests that from 2005-2007, there were 7 900 000 annual prescriptions for antiepileptic medications among girls and women aged 15 to 44 years, including 926 000 for valproate (12% of all antiepileptic medication prescriptions, irrespective of indication).[1] For those treated for epilepsy or seizures, there were 989 000 annual prescriptions, of which 177 000 were for valproate (18% of all prescriptions of antiepileptic medications for epilepsy or seizures).[1]

After multiple pregnancy registries confirmed an increased risk of major congenital malformations following fetal valproate exposure, the American Academy of Neurology recommended avoidance of valproate during pregnancy whenever possible.[2] In addition to the risk of congenital malformations, fetal valproate exposure has been associated with reduced cognitive abilities,[2,3] which led the US Food and Drug Administration to issue a warning about this risk.[4] Further, several studies have suggested that fetal valproate exposure may increase the risk of autism,[5-8] although the strength of this association has been unclear because of the methodological limitations of those reports.

In this issue of *JAMA*, Christensen and colleagues[9] report the results of a population-based study of 655 615 children born in Denmark from 1996 to 2006. Among these children, 5437 were identified as having autism spectrum disorder, including 2067 with childhood autism. When examining the relationship of fetal valproate exposure to developmental outcome, increased risks of autism spectrum disorder (absolute risk, 4.42%; adjusted hazard ratio, 2.9 [95% CI, 1.7-4.9]) and childhood autism (absolute risk, 2.50%; adjusted hazard ratio, 5.2 [95% CI, 2.7-10.0]) were observed among the 508 children exposed to valproate. The authors concluded that maternal use of valproate during pregnancy was associated with significantly increased risks of autism spectrum disorder and childhood autism in the offspring and that those risks remained significant after restricting the analysis to children without congenital malformations and after adjusting for parental psychiatric disease and epilepsy. This important information should be presented during the counseling of women of childbearing potential when discussing treatment options that include valproate.

The investigation by Christensen et al[9] provides the strongest evidence to date that fetal valproate exposure is associated with increased risks of autism and autism spectrum disorder. Strengths of the study include that it was population-based, provided follow-up for

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a very large cohort for 14 years, and had less than 3% loss to follow-up, thus reducing the risk of selection bias. In the analysis, the authors adjusted for a large number of potentially confounding risk factors for autism. Separating the effects of the drug from the underlying disease and related genetic factors can be difficult. However, confidence that the observed risks are related to valproate exposure is increased by the findings that the risk of valproate exposure did not differ across maternal disease (ie, epilepsy vs no epilepsy) and that the children of women who had previously used valproate and stopped it at least 30 days prior to conception were not at increased risk for autism.

Limitations of the study by Christensen et al include inadequate information about periconceptional use of folate and use of folate later in pregnancy, use of alcohol or illicit drugs during pregnancy, and possible missed psychiatric diagnoses in the parents. Other antiepileptic medications were analyzed, but there was no adjustment in the analyses for prescriptions of other drug types. An insufficient number of women took valproate only in late pregnancy to allow determination of differential risk across trimesters. The study did not find that higher doses of valproate were associated with higher risk of autism, but the doses of valproate were inferred from prescriptions filled, and information on the actual doses taken was not available. In addition, there were no measures of medication adherence or blood levels of valproate. In contrast, multiple studies have found that the risks of malformations and reduced cognitive abilities are increased at higher doses of valproate, which would be expected of a teratogen.[2,3,10,11] It is unclear if there is a safe dose.

The risk of autism adds to the other risks of fetal valproate exposure.[2] A meta-analysis estimated that 10.7% of children exposed in utero to valproate develop major congenital malformations.[10] Most studies have examined overall risks of major malformations combined because demonstration of specific defects requires larger samples. However, the increased risk for spina bifida from fetal valproate exposure has been recognized for 3 decades.[12] Further, a recent large study from the European Surveillance of Congenital Anomalies (EUROCAT) reported that use of valproate monotherapy was associated with significantly increased risks for 6 specific malformations: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis.[13] A recent large prospective study of cognitive outcomes at age 6 years among children with fetal antiepileptic medication exposure found that those exposed to valproate had IQs that were on average 7 to 10 points lower compared with children exposed to 3 other antiepileptic medications, and a range of cognitive domains were impaired in the valproate group, including language, nonverbal, and memory and executive functions.[11]

Valproate is an effective treatment, not only for seizures but also for pain and bipolar disorder as well as other disorders. Less than 20% of valproate prescriptions are for treatment of epilepsy or seizures in girls and women aged 15 to 44 years.[1] However, other therapeutic options are available for the majority of women with these disorders. Knowledge of the risks posed by fetal exposure is limited for many drugs used to treat seizures, pain, and bipolar disorder, but data for several medications used in each disorder indicate that the risks associated with their use are substantially less than those for valproate.

Despite the established risks of fetal valproate exposure, valproate continues to be a common treatment in women of childbearing age.[14,15] Valproate is an effective drug, but it appears that it is being prescribed for women of child-bearing potential at a rate that does not fully consider the ratio of benefits to risks. This raises concern as to whether these women are receiving adequate information for informed consent based on a full understanding of the treatment risks and alternative therapies. Given the accumulating evidence linking fetal valproate exposure to congenital malformations, cognitive impairments, and autism, the use of valproate in women of childbearing potential should be

minimized. Alternative medications should be sought. If no alternative effective medications can be found, the lowest effective dose of valproate should be used. Because approximately half of the pregnancies in the United States are unplanned, delaying discussions of treatment risks until a pregnancy is considered will leave a substantial number of children at unnecessary risk. Women of childbearing potential should be informed of the potential risks of fetal valproate exposure before valproate is prescribed.

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