Use of anti-epileptic drug during pregnancy associated with increased risk of autism

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Maternal use of valproate (a drug used for the treatment of epilepsy and other neuropsychological disorders) during pregnancy was associated with a significantly increased risk of autism in offspring, according to a study in the April 24 issue of *JAMA*. The authors caution that these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

"Anti-epileptic drug exposure during pregnancy has been associated with an increased risk for congenital malformations and delayed cognitive development in the offspring, but little is known about the risk of other serious neuropsychiatric disorders," according to background information in the article.

Jakob Christensen, Ph.D., of Aarhus University Hospital, Aarhus, Denmark, and colleagues evaluated the association between maternal use of valproate during pregnancy and the risk of autism spectrum disorder and childhood autism in offspring. The population-based study included all children born alive in Denmark from 1996 to 2006. National registers were used to identify children exposed to valproate during pregnancy and diagnosed with autism spectrum disorders (childhood autism [autistic disorder], Asperger syndrome, atypical autism, and other or unspecified pervasive developmental disorders). Data were analyzed and adjusted for potential confounders (factors that can influence outcomes) such as maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity. Children were followed up from birth until

the day of autism spectrum disorder diagnosis, death, emigration, or December 31, 2010, whichever came first.

The analysis included 655,615 children born from 1996 through 2006. The average age of the children at end of follow-up was 8.8 years. During the study period, 5,437 children were diagnosed with autism spectrum disorder, including 2,067 with childhood autism. The researchers identified 2,644 children exposed to antiepileptic drugs during pregnancy, including 508 exposed to valproate. The authors found that use of valproate during pregnancy was associated with an absolute risk of 4.42 percent for autism spectrum disorder and an absolute risk of 2.50 percent for childhood autism.

"In this population-based cohort study, children of women who used valproate during pregnancy had a higher risk of autism spectrum disorder and childhood autism compared with children of women who did not use valproate. Their risks were also higher than those for children of women who were previous users of valproate but who stopped before their pregnancy," the researchers write.

"Because autism spectrum disorders are serious conditions with lifelong implications for affected children and their families, even a moderate increase in risk may have major health importance. Still, the absolute risk of autism spectrum disorder was less than 5 percent, which is important to take into account when counseling women about the use of valproate in pregnancy."

Kimford J. Meador, M.D., and David W. Loring, Ph.D., of Emory University, Atlanta, write in an accompanying editorial that "women of childbearing potential should be informed of the potential risks of fetal valproate exposure before valproate is prescribed."

"Despite the established risks of fetal valproate exposure, valproate

continues to be a common treatment in women of childbearing age. 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."

More information: *JAMA*. 2013;309(16):1696-1703
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