



Does in utero exposure to valproate increase the risk of autism?

Yes. Children exposed to the drug in utero had a significantly increased risk of autism spectrum disorder and childhood autism, even after adjustment for maternal epilepsy, according to this population-based study of all live births in Denmark from 1996 to 2006.

Valproate is indicated not only for the treatment of epilepsy, but also for manic episodes associated with bipolar disorder and for prophylaxis of migraine headaches.

Christensen J, Gronborg TK, Sorensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013;309(16):1696-1703.

►EXPERT COMMENTARY

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In utero exposure to valproate (VPA) is associated with a 6% to 10% risk of major congenital malformations, including spina bifida and hypospadias.¹ These risks are linked to first-trimester exposure and are dose-dependent, with daily doses below 750 mg carrying a 4% risk of malformation, and daily doses above 2,000 mg carrying a risk of about 20%.²

Cognitive teratogenesis in offspring exposed to VPA in utero also has been described,³ and an association between VPA and autism spectrum disorder (ASD) has been suspected, but convincing data have not been published until now. This population-based, retrospective study using Danish national medical registers identified children with ASD or childhood autism and determined the

independent risk of these disorders associated with in utero exposure to VPA.

The issue of cognitive teratogenesis in VPA-exposed children has evolved since the initial recognition, in 2001, that these offspring have increased educational needs.⁴ An association between in utero exposure to VPA and ASD was first described in 2008 by Bromley and colleagues, who reported that 6.3% (4/64) of VPA-exposed children developed the disorder—a sevenfold increase in the expected rate of autistic features.⁵

WHAT THIS EVIDENCE MEANS FOR PRACTICE

These findings confirm earlier data and support the accepted practice of avoiding the prescription of valproate for women of reproductive potential, if at all possible. They do not support the possibility that a judicious dose or careful timing during pregnancy increases the safety of this drug in regard to autism. Although its absolute risk is less than 5%, autism may be associated with severe, lifelong disability. Therefore, I recommend that providers make every attempt to avoid giving valproate to women during preconception and pregnancy.

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**FAST
TRACK**

Avoid prescribing valproate for women of reproductive potential, if at all possible

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Details of the study

Christensen and colleagues reviewed the records of all live births in Denmark from 1996 to 2006, using national registers to identify children who were exposed to VPA in utero and later given a diagnosis of ASD or childhood autism. These children were followed from birth until the diagnosis of ASD or childhood autism, death, emigration, or December 31, 2010, whichever came first.

Investigators adjusted for potential confounders:

- maternal age at conception
- paternal age at conception
- parental psychiatric history
- gestational age
- birth weight
- sex
- congenital malformations
- parity.

Other important variables evaluated by the investigators include maternal epilepsy, use of other antiepileptic drugs, and antiepileptic drug polytherapy.

Among VPA-exposed children (n = 508), the absolute risk of ASD was 4.42%, and the absolute risk of childhood autism was 2.95%. By comparison, in the overall population (n = 655,107), the absolute risks of ASD and childhood autism were 1.53% and 0.48%, respectively.

No other antiepileptic drugs were associated with an increased risk of these disorders, and maternal epilepsy itself did not increase their risk significantly.

In contrast to the risk of structural teratogenesis, which varies by the trimester of exposure and the dose of VPA, investigators

found no association with trimester of exposure or dose in regard to ASD and childhood autism. **In other words, there is no safe time in pregnancy to stop or start valproate and no safe dose of valproate in pregnancy to mitigate the risk of autism.**

Strengths and limitations

This is a convincing and impressively performed study. The only limitations are its retrospective nature (although the investigators adjusted for the increase in the expected background occurrence of autism during the study period) and the issues inherent in a population based study:

- Is the national database entry accurate?
- Is this population the same as the population I am interested in?

We are presuming that the answer to both questions is “Yes.” ☺

References

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