Published in final edited form as:

J Pediatr. 2013 September ; 163(3): 924. doi:10.1016/j.jpeds.2013.06.050.

Prenatal valproate exposure is associated with autism spectrum disorder and childhood autism

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Question

Controlling for known risk factors, what is the association of prenatal valproate exposure with development of autism spectrum disorder or childhood autism, compared with unexposed children?

Design

Prospective, population-based birth cohort study.

Setting

Denmark.

Participants

All children born 1996–2006.

Intervention

Prenatal valproate.

Outcomes

Autism spectrum disorder and childhood autism.

Main Results

Of 655 615 children born from 1996 through 2006, 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. The mean age of the children at end of follow-up was 8.84 years (range, 4–14; median, 8.85). The estimated absolute risk after 14 years of follow-up was 1.53% (95% CI, 1.47%–1.58%) for autism spectrum disorder and 0.48% (95% CI, 0.46%–0.51%) for childhood autism. Overall, the 508 children exposed to valproate had an absolute risk of 4.42% (95% CI, 2.59%–7.46%) for autism spectrum disorder, adjusted hazard ratio (HR), 2.9 (95% CI, 1.7–4.9) and an absolute risk of 2.50% (95% CI, 1.30%–4.81%) for childhood autism, adjusted HR, 5.2 (95% CI, 2.7–10.0). When restricting the cohort to the 6584 children born to women with epilepsy, the absolute risk of autism spectrum disorder among 432 children exposed to valproate was 4.15% (95%

CI, 2.20%–7.81%), adjusted HR, 1.7 (95% CI, 0.9–3.2), and the absolute risk of childhood autism was 2.95% (95% CI, 1.42%–6.11%), adjusted HR, 2.9 (95% CI, 1.4–6.0) vs 2.44% (95% CI, 1.88%–3.16%) for autism spectrum disorder and 1.02% (95% CI, 0.70%–1.49%) for childhood autism among 6152 children not exposed to valproate.

Conclusions

Maternal use of valproate during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring, even after adjusting for maternal epilepsy. For women of childbearing potential who use antiepileptic medications, these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

Commentary

Christensen et al present strong evidence that fetal valproate exposure is associated with increased risks of autism and autism spectrum disorder. Study strengths include the large population-based cohort, extended longitudinal follow-up, very few subjects lost to follow-up, and analyses adjusting for many potentially confounding factors. Limitations include inadequate information on folate, alcohol or illicit drugs use, no adjustments for other prescribed drugs, and lack of measures for medication compliance or valproate blood levels. In addition to autism risk, fetal valproate exposure has been associated with a number of specific congenital malformations,¹ and with cognitive impairment even in the absence of malformations.^{2,3} Fetal valproate exposure is also associated with reduced IQ (7–10 points) compared with other antiepileptic drugs, and exhibits dose-dependent adverse effects across a range of cognitive domains.³ Valproate is commonly used in women of childbearing age for seizures, pain, and psychiatric disorders. Given the established risks of fetal valproate exposure, clinicians should inquire about possible fetal valproate exposure in children with cognitive or behavioral problems, including autism. Clinicians should carefully screen children with a history of fetal valproate exposure for anatomical defects and neuropsychologic impairments in order to detect abnormalities and institute appropriate interventions.

References

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