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Maternal folic acid supplements associated with reduced autism risk in the child

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Commentary on: Surén P, Roth C, Bresnahan M, *et al*. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. *JAMA* 2013;309:570–7.

Context

Autism spectrum disorder (ASD) prevalence is increasing. Maternal periconceptional folic acid intake was associated with reduced ASD risk in a large, population-based case-control study.¹ Surén and colleagues examined whether maternal folic acid supplements were associated with reduced risk for ASD.

Methods

The Norwegian Mother and Child Cohort Study (MoBa) included 85 176 children at least 3 years old born between 1999 and 2009. Questionnaire information on maternal supplement use was obtained around 18-week gestation.

Findings

The 270 MoBa children diagnosed with ASD included 114 with autistic disorder, 56 with Asperger syndrome and 100 with pervasive developmental disorder, not otherwise specified (PDD-NOS). Of the 61 042 children whose mothers took folic acid from 6 weeks before to 6 weeks after conception, 64 (0.10%) had autistic disorder, compared with 50 (0.21%) of the 24 134 children whose mothers did not (adjusted OR 0.61, 95% CI 0.41 to 0.90). Associations were not found for Asperger syndrome or PDD-NOS.

Commentary

This study replicates previous findings^{1 2} that folic acid supplements taken by mothers before and during early pregnancy are associated with lower risk for autism in the child. The prospective design had a major advantage over previous case-control studies; reporting of supplement use occurred before outcomes were known. Thus recall bias that can occur when case mothers remember past exposures with different accuracy than control mothers was avoided. Another key difference between this and earlier studies is that Norway does not fortify foods with folic acid; previous studies were conducted in the USA during periods of mandatory fortification of cereal grains. In addition, supplements reportedly contained lower folic acid levels (400 µg) than those in the USA (800 µg).² Finally, this study's critical exposure window overlapped, but differed slightly from that of previous studies.^{1 2} Remarkably, despite differences between studies, the authors reported nearly the exact effect size for periconceptional folic acid supplement intake, showing a nearly 40% reduction in autism risk. Despite the large cohort size and multimode approach

for ascertaining cases, this study included a small number of children with ASD. As the authors note, this limited examination of differences by case subtypes, and could have introduced ascertainment bias, likely towards the null. ASD prevalence in MoBa (0.3%) was less than half what they reported for Norway (0.8%), indicating markedly incomplete ascertainment, especially for children with Asperger syndrome and PDD-NOS. In addition, only 50% of cases were clinically assessed; the rest relied on specialist-confirmed Norwegian Patient Registry diagnoses that were less reliable for ASD subtypes. These limitations suggest that the findings for at least the ASD subtypes should be interpreted cautiously. Additionally, the authors excluded children with birth outcomes that could be on the pathway between periconceptional folic acid intake and ASD, which likely biased the association towards the null.

Quantitative information on dietary folate and supplemental folic acid was available for mothers at gestational week 22, but not earlier during the relevant exposure period. Consequently, the authors were unable to examine the impact of dietary intake during this time, and ASD risk at different levels of folic acid to replicate the previously shown inverse dose-trend. Effects of maternal and child genotypes that significantly influence folate metabolism and ASD risk^{1 2} were also not evaluated.

Causality for the link between periconceptional folic acid and 50–70% fewer neural tube defects (NTDs) was established through randomised clinical trials. Observational cohort studies have shown associations with reduced risk for severe language delay, behavioural and peer problems, and childhood hyperactivity, and with improved verbal and verbal-executive function, attention and social competence.¹

Whether the association with autism is causal and what mechanisms are involved remain to be determined. Nevertheless, the overall consistency across studies, and the known protection against NTDs, and potentially other pregnancy and developmental outcomes, argue strongly for women of childbearing age to follow current recommendations to take folic acid supplements before and during early pregnancy. No known adverse conditions are associated with first trimester maternal folic acid at the recommended levels. The proportion of women who started taking folic acid-containing supplements before pregnancy was low in both the USA (45%) and Norwegian (33%)

studies, despite the majority of women reporting their pregnancy as planned (70% and 80%, respectively). Current recommendations regarding early initiation of folic acid supplementation need to be more effectively delivered to the general public.

Competing interests None.

References

1. Schmidt RJ, Tancredi DJ, Ozonoff S, *et al*. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. *Am J Clin Nutr* 2012;**96**:80–9.
2. Schmidt RJ, Hansen RL, Hartiala J, *et al*. Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. *Epidemiology* 2011;**22**:476–85.