Does high-dose gestational folic acid increase the risk for autism? The birth order hypothesis

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A B S T R A C T

There has been a dramatic increase in the incidence of autism spectrum disorder (ASD) in recent decades but the causes have not been elucidated. To date, numerous studies have shown that the FDA-recommended doses of folic acid (400 mcg/d) render a protective effect against ASD. Yet, a recent prospective study has claimed that while self-reported folic acid supplementation was associated with decreased risk of ASD, very high levels of maternal plasma folate levels (< 60.3 nmol/L) were associated with 2.5 time increased risk of ASD. This study has led to high levels of public anxiety because many women use high dose folic acid to prevent neural tube defects.

We hypothesize that because ASD children have been documented to be much more likely to be first or second born, and women consume significantly more folic acid during their first and second pregnancies, the claim that high dose folic acid causes ASD is based on a previously unrecognized birth order bias.

This article presents evidence for the wrong claim that high dose folic acid causes ASD. The question whether high exposure level of folic acid is associated with increased risk of ASD is not merely a theoretical issue, because many women at increased risk for NTD in their offspring need substantially higher daily doses of folic acid (1 mg, or 5 mg), than the FDA-recommended 400 mcg daily.

Background

There has been a dramatic increase in the incidence of autism spectrum disorder (ASD) in recent decades [1–3]. This increased prevalence has been partially attributed to increased awareness, earlier detection, older parental age and changes in ASD definition over time [4]. However the main cause for the 3–4 fold increased incidence has not been identified. A wide search for environmental factors leading to, or contributing to ASD has included folic acid supplementation, as there has been a tremendous growth in numbers of women receiving folic acid for the prevention of neural tube defects (NTD), which has been temporally parallel to the increasing incidence of ASD. However, numerous studies examining this question have clearly shown that the FDA-recommended doses of folic acid (400 mcg/d) appear to render a protective effect against ASD [5–8] when compared to women not supplementing with folic acid prenatally.

In contrast, there have been several papers offering a hypothetical framework as to why excess folic acid may increase the risk for ASD [9,10]. In 2018 Raghavan and colleagues published a prospective cohort of 1257 mother-child pairs, examining potential associations between folic acid use and the risk of ASD [11]. ASD diagnoses were extracted from electronic medical records and maternal multivitamin supplementation was collected through interviews. Similar to previous studies, they have shown that moderate (3–5 times/week) self-reported folic acid supplementation was associated with decreased risk of ASD. However, they have also measured maternal plasma folate at birth and reported that very high levels of maternal plasma folate levels (< 60.3 nmol/L) were associated with 2.5 time increased risk of ASD [11]. Intuitively, measuring levels appears to render more credibility to the evidence at hand and hence, to potentially overcome the “association/no causation” hurdle. Indeed, this study has led to high levels of public anxiety [12,13]. The question whether high exposure level of folic acid is associated with increased risk of ASD is not merely a theoretical issue, because many women at increased risk for NTD in their offspring are encouraged to consume substantially higher daily doses of folic acid (e.g. 1 mg, or 5 mg), than the FDA-recommended 400 mcg daily. These include mothers of previously affected children by NTD, women receiving antiepileptic drugs and other anti-folate agents (e.g. sulfonamides, methotrexate), as well as women with certain metabolic aberrations in folate metabolism [14].

The hypothesis

Recent findings shed a whole new light on this enigma and, we believe, helps to resolve it [15]. It has been known that children with ASD are significantly more likely to have a lower birth order (i.e. to be the first or second born...
Consequences of the hypothesis

The evidence presented herein identifies a new source of bias not previously recognized, i.e. the effect of birth order on folic acid use in pregnancy, combined with the fact that children with ASD are significantly more likely to be first born. The recognition of this hypothesis is of public health importance given that folic acid is needed to prevent up to 75% of neural tube defects, sometimes with the need high doses. Increase in women's anxiety about using folic acid preconceptionally [12,13] may lead women not to use folic acid prior to conception, and hence loosing an opportunity to prevent a major and debilitating birth defect.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References