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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 (400mcg/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 Raghhavan 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

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rather than later children in the family) [16], because after an affected child is born, the likelihood of the family of having a subsequent child is substantially decreased. This effect has been dubbed the "stoppage effect" [17].

A new study [15] has documented, using a very large computerized database with 578,204 children and their 228,555 mothers, that the total dose of folic acid purchased 12 months prior to child birth was much larger among nulliparous mothers (120 mg, 95% CI 48–240) than by women with one (90 mg, 39–202), or two pregnancies (84 mg, 36–182(11)). The dose was even lower among women with 3 or more prior births (75 mg, 36–165). This study strongly documents improved adherence to folic supplementation during the first pregnancies [15]. Hence, not surprising, first born children are significantly more likely to have higher exposure levels of folic acid due to substantially higher maternal intake. If, independently, the first or second child also have higher rates of ASD due to the "stoppage effect" described above [16,17], then the birth order becomes a source of uncontrolled bias in supporting the view that high folate levels may be the cause of ASD.

Evaluation of the hypothesis

The hypothesis introduced here suggests that high levels of exposure to folic acid is due to the fact that first born children are much more likely to receive more folic acid, and that ASD children are much more likely to be first born. However, these 2 pieces of evidence have emerged from different cohorts and, therefore, can suggest an association, but cannot prove causation. In other words: despite the association of birth order with both diagnosis of ASD and high folate exposure, it is still also possible that excess folic acid may damage brain development and cause ASD as several hypothetical framework articles have suggested [9,10]. Hence, to further prove our hypothesis, the birth order effect must be tested in the same cohort, looking at both maternal folate intake and odds ratio of autism. A study fulfilling these requirements has just been published and can further support our hypothesis [18]:

In a large health fund insuring 2 million citizens, all singleton ASD cases diagnosed among 504,028 children born between 2000 and 2010 (inclusive) (n = 2009) were matched with up to 10 non autistic controls (n = 19,886). The cumulative mean dose of supplemented folic acid dispensed during the 12 months preceding birth was compared between the ASD and healthy groups using conditional multivariable logistic regression.

As expected [16,17], significantly more autistic children were first born, and birth order was independently and significantly associated with folic acid use: Mothers purchased significantly more folic acid during the first pregnancy than during later pregnancies. In multivariable analysis, accounting for birth order and other confounders, folic acid use was not associated with increased autistic risk, and no dose-response trends were observed.

Important for our hypothesis, the lack of association between folic acid dose and occurrence of ASD was further confirmed in sensitivity analysis restricted to first-born boys (1107 ASD cases, 1107 controls), while adjusting for all other variables. The results were in agreement with the main analysis, suggesting a null association of folic acid use with ASD risk (OR 0.99, 95% confidence interval 0.41, 2.42) [18].

While we hypothesize that excess folic acid is not a cause of ASD, recent animal work has suggested that folate deficiency is associated with neurodevelopmental disorders such as neural tube defects and hydrocephalus. 10-formyl-tetrahydrofolate-dehydrogenase (FDH) is a key regulator for folate availability and metabolic interconversion for the supply of 1-carbon groups. Deficiency of FDH in the cerebrospinal fluid has been associated in rats with the developmental deficit in congenital and neonatal hydrocephalus [19]. This experimental work further supports our hypothesis that deficits, and not excess in folic acid is a cause of neurodevelopmental deficits.

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 pre conceptionally [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

[1] Blumberg SJ, Bramlett MD, Kogan MD, et al. Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007 to 2011–2012. Natl Health Stat Report 2013;20(65):1–11.
[2] Christensen DL. Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveill Summ 2016;65.
[3] Davidovitch M, Hemo B, Manning-Courtney P, et al. Prevalence and incidence of autism spectrum disorder in an Israeli population. J Autism Dev Disord 2013;43(4):785–93.
[4] Matson JL, Kozlowski AM. The increasing prevalence of autism spectrum disorders. Res Autism Spectrum Disorders 2011;5(1):418–25.
[5] 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(1):80–9.
[6] 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(6):570–7.
[7] Virk J, Liew Z, Olsen J, et al. Preconceptional and prenatal supplementary folic acid and multivitamin intake and autism spectrum disorders. Autism 2016;20(6):710–8.
[8] Steenweg-de Graaff J, Ghassabian A, et al. Folate concentrations during pregnancy and autistic traits in the offspring. The Generation R Study. Eur J Publ Health 2015;25(3):431–3.
[9] Beard CM, Panser LA, Katusic SK. Is excess folic acid supplementation a risk factor for autism? Med Hypothesis 2011;77(1):15–7.
[10] Rogers EJ. Has enhanced folate status during pregnancy altered natural selection and possibly Autism prevalence? a closer look at a possible link. Med Hypothesis 2008;71(3):406–10.
[11] Raghavan R, Riley AW, Volk H, et al. Maternal multivitamin intake, plasma folate and vitamin B12 levels and autism spectrum disorder risk in offspring. Paediatr Perinat Epidemiol 2018;32(1):100–11. https://doi.org/10.1111/ppe.12414. Epub 2017 Oct 6.
[12] Too much folic acid in pregnancy tied to raised autism risk http://www.webmd.com/baby/news/20160511/too-much-folic-acid-in-pregnancy-tied-to-raised-autism-risk-in-study#1. Accessed June 11, 2019.
[13] Too-much-folate-pregnant-autism https://hub.jhu.edu/2016/05/12/too-much-folate-pregnant-autism/ Accessed June 12, 2019.
[14] Chitayat D, Matsui D, Amitai Y, et al. Folic acid supplementation for pregnant women and those planning pregnancy: 2015 update. J Clin Pharmacol 2016;56:170–5.
[15] Sharman Moser S, Rabinovitch M, Rotem R, et al. Parity and the use of folic acid supplementation during pregnancy. BMJ NPH 2019:1–5. https://doi.org/10.1136/bmjnph-2019-000024.
[16] Durkin MS, Maenner MJ, Newschaffer CJ, et al. Advanced parental age and the risk of autism spectrum disorder. Am J Epidemiol 2008;168(11):1268–76. https://doi.org/10.1093/aje/kwn250. Epub 2008 Oct 21.
[17] Slager SL, Foroud T, Haghighi F, et al. Stoppage: an issue for segregation analysis. Genet Epidemiol 2001;20(3):328–39.
[18] Sharman Moser S, Rotem R, Davidovich M, et al. Folic acid during pregnancy and the risk of autism; the birth order bias; a nested case control study. Reprod Toxicol 2019. in press.
[19] Naz N, Requena Jimenez A, Gurney M, et al. Neonatal hydrocephalus is a result of a block in folate handling and metabolism involving 10-formyltetrahydrofolate dehydrogenase. J Neurochem 2016;138(4). https://doi.org/10.1111/jnc.13686.