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Think Beyond Malformations: The Case for Periconceptional Folate in Women With Epilepsy

Effects of Periconceptional Folate on Cognition in Children of Women With Epilepsy: NEAD Study

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Objective: Emerging evidence suggests potential positive neuropsychological effects of periconceptional folate in both healthy children and children exposed in utero to anti-seizure medications (ASMs). In this report, we test the hypothesis that periconceptional folate improves neurodevelopment in children of women with epilepsy by reexamining data from the neurodevelopmental effects of antiepileptic drugs (NEAD) study. Methods: The NEAD study was a National Institute of Health-funded, prospective, observational, multicenter investigation of pregnancy outcomes in 311 children of 305 women with epilepsy treated with ASM monotherapy. Missing data points were imputed with Markov chain Monte Carlo methods. Multivariate analyses adjusted for multiple factors (eg, maternal intelligence quotient [IQ], ASM type, standardized ASM dose, and gestational birth age) were performed to assess the effects of periconceptional folate on cognitive outcomes (ie, full scale intelligence quotient [FSIQ], verbal and nonverbal indexes, and expressive and receptive language indexes at 3 and 6 years of age, and executive function and memory function at 6 years of age). Results: Periconceptional folate was associated with higher FSIQ at both 3 and 6 years of age. Significant effects for other measures included nonverbal index, expressive language index, and developmental neuropsychological assessment executive function at 6 years of age, and verbal index and receptive language index at 3 years of age. Nonsignificant effects included verbal index, receptive index, behavior rating inventory of executive function-parent questionnaire executive function, and general memory index at 6 years of age, and nonverbal index and expressive index at 3 years of age. Conclusions: Use of periconceptional folate in pregnant women with epilepsy taking ASMs is associated with better cognitive development.

Commentary

The benefits of periconceptional use of folic acid during pregnancy in the general population are well recognized. Folic acid intake is associated with a decreased risk of major fetal malformations (MFMs) including neural tube defects,[1] limb malformations, cleft lip and palate, structural cardiac disease, and urogenital malformations. These malformations have a broad range of severity from mild and purely cosmetic to incompatible with life. Different doses of folic acid are recommended to women planning for pregnancy, undergoing fertility treatment, and more broadly to all women of childbearing age by some practices.[2]

The benefit of folic acid supplementation in reducing risk of MFM in women with epilepsy (WWE) is less clear. Multiple prospective pregnancy studies have evaluated the effects of specific anti-seizure medications (ASMs) in relation to the presence of MFM at birth.[3] These studies have not established whether the use of folic acid specifically decreases the risk of MFM in this specific population. However, there is some suggestion that it may reduce the risk of fetal loss.[4] Extrapolating from the knowledge in the general population, WWE are routinely prescribed folic acid while trying for pregnancy, with a variable dose ranging from 0.4 to 4 mg a day.

Looking beyond the effects of ASM on MFM, the neurodevelopmental effects of antiepileptic drug (NEAD) study[5] was designed as a prospective observational cohort to blindly evaluate structured neurocognitive outcomes of the offspring of WWE exposed to ASM in utero. Neuropsychological assessments were conducted in the children up to the age of 6 years. The NEAD results were only reported for children exposed to carbamazepine, phenytoin, lamotrigine, and valproic acid, as the number of women exposed to other ASM were not robust enough to draw conclusions. All pregnancies enrolled were exposed to ASM, so there is no control group in this study.

The present study by Meador et al[6] is a subanalysis of the data presented from the NEAD study. It analyzed the effects of preconceptional folate in regard to specific cognitive outcomes as defined by structured sequential neuropsychological testing

performed in these children aged from 3 to 6 years. Both the length of follow-up and the use of objective neurocognitive measures, beyond the subjective parental report, are this study's strengths. The results show benefit of the use of preconceptional folate expressed as higher full scale intelligence quotient (FSIQ), better performance on nonverbal and verbal tasks, and some measures of executive function, even after controlling for other variables such as maternal IQ. Other neuropsychological measures of executive and memory functions were reported as not affected by preconceptional folate intake. It is interesting to notice that all ASM included in the analysis interfere with the metabolism of folic acid and have been described to decrease its blood levels.[7] This interaction makes studying the exposure to folic acid as an independent factor in this population challenging. But the results presented by Meador et al support the use of folic acid supplementation in WWE of childbearing age beyond its possible effects on MFM.

A positive effect of folic acid in neurodevelopment has been suggested before. The Norwegian Mother and Child Cohort Study[8] found that the use of periconceptional folic acid intake and higher folate plasma levels to reduce the risk of autistic traits and improve language development in the children of WWE on ASM at 18 and 36 months of age.[9] This relation was not significant in women without epilepsy or WWE not taking ASM, suggesting folic acid may merely mitigate the effects of ASM in neurodevelopment. It is important to notice that at the time of the study, Norway did not require food to be fortified with folic acid.

The variability of the dose of folic acid recommended for WWE is interesting, more so if we take into account some practical considerations: Different world populations may receive variable doses of folic acid though their diet. Women in the United States receive a dose of folic acid in the form of "fortified foods," which includes grain products such as pasta, cereal, bread, and rice following a Food and Drug Administration(FDA) requirement in 1998. The Center for Disease Control and prevention (CDC) reports the prevalence of neural tube defects at birth to be reduced by 35% since that time. Commercial preparations of women multivitamin in the United States typically include 0.4 mg of folic acid, prenatal vitamins 0.8 mg, and prescription folic acid is usually in the form of 1 mg tablets. The standard American diet or any supplementation including folate results in intake higher than 0.4 mg, which is the threshold dose described as beneficial to neurocognitive outcome in offspring of WWE in the NEAD study.

The question of how much folic acid to recommend to WWE has not been settled yet. Just as we mentioned how folic acid supplementation during pregnancy can be beneficial to children's neurodevelopment, high doses (>5 mg a day) of folate are reported to be associated with lower psychomotor scores and delayed psychomotor development compared to children born to women who were taking lower doses (0.4-1 mg).[10] One confounding factor may be that mothers with higher risk pregnancies may be encouraged to take larger folic acid doses. In addition, high doses of folic acid may lower levels of some ASM, lower seizure threshold, and negatively affect brain development of offspring in animal models.[11]

Specific counselling regarding pregnancy risks in relation to epilepsy and ASM, interactions of birth control therapies and ASM, and management of ASM during pregnancy and after delivery, among other gender-related issues in epilepsy is standard of care for WWE. It is well established that most pregnancies in women with or without epilepsy are not planned. Preconceptional care has shown to improve seizure control during pregnancy and increase folic acid intake[12]; however, it has not shown to decrease the risk for MFM, bringing back the argument that the rate of MFM in WWE is likely more related to the choice of ASM than the use of folic acid, in contrast to the general population. The possibility of folic acid improving long-term cognitive outcome in children born to WWE strengthens the case for the recommendation to take folic acid at a dose between 0.4 and 4 mg a day in the periconceptional period and throughout the pregnancy. Although the optimal dose and the real effects of folic acid regarding MFM in WWE on specific ASM are still not clear at this time, there is emerging evidence that the use of periconceptional folic acid improves neurodevelopmental outcomes in children born to WWE who were exposed to ASMs during pregnancy. Thus, there is a benefit beyond the potential impact on malformations which makes it a worthwhile intervention.

By Adriana Bermeo-Ovalle

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ORCID iD

Adriana Bermeo-Ovalle https://orcid.org/0000-0003-2346-0061

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