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Strategies for Preventing Folate-Related Neural Tube Defects: Supplements, Fortified Foods, or Both?

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The finding in 1991 that women who took folic acid supplements prior to conception reduced their risk for having a child with spina bifida or other neural tube defects (NTDs) by more than 50% stimulated an immediate effort to implement this discovery at the population level.¹ This effort proved difficult because the neural tube closes by the 28th day after conception, before many women know they are pregnant, and so women may need to begin taking folic acid well before conception.

In 1992, the US Public Health Service (USPHS) recommended that all women of childbearing age capable of becoming pregnant take 400 µg of folic acid per day.² The rationale for this broad recommendation was that approximately half of pregnancies are unplanned.³ In 2009, the US Preventive Services Task Force (USPSTF) first recommended that all women planning or capable of pregnancy take 400 to 800 µg of folic acid daily.⁴ In this issue of *JAMA*, the updated USPSTF recommendation statement reaffirms that position: “The USPSTF recommends that all women who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 µg) of folic acid (A recommendation).”⁵ This recommendation differs from the USPHS recommendation in suggesting a range of folic acid as the target dose. However, some of the most important current issues, such as evaluating the role of food fortification, were not part of the charge of the USPSTF.

Many of the USPHS committee members were aware that the recommendation that women take supplements daily would be unlikely to prevent all folate-related NTDs for several reasons: women not planning a pregnancy might not adhere; it would be costly to purchase the tablets; and it would be an inconvenience to take folic acid daily for 30 years. Despite public information campaigns, only about 40% of the women at risk followed the recommendation to take supplements daily.⁶

Indeed, in countries that have continued to rely primarily on this supplement-taking approach with some voluntary food fortification, as in the European Union, the results have

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been disappointing. Most areas have not experienced a significant decrease in NTD rates from 1991 to 2011.⁷

Because many women remained at risk for having children with folate-related NTDs, the US government decided to institute mandatory food fortification with folic acid in 1996. All enriched cereal grains were required to contain 140 µg of folic acid per 100 g of grain by January 1998.⁸ This strategy has been adopted by approximately 80 countries,⁹ with remarkable success. Data from many countries showed a significant decline in NTD rates after mandatory fortification.¹⁰

Mandatory fortification has the important advantage that all women who consume enriched cereal grain receive some folic acid. The disadvantage is that, unlike taking folic acid supplements, the entire population is exposed, an issue that has caused considerable debate in the European Union.¹¹ Concerns have been expressed regarding the possibility that exposure to high doses of folic acid might cause an increased risk of cancer, asthma, cognitive problems, twin pregnancy, and autism and may mask vitamin B₁₂ deficiency anemia; however, the data published to date do not confirm any of these harms, with the exception of masking of vitamin B₁₂ deficiency anemia in elderly persons. Nonetheless, it is prudent to seek the lowest dose of folic acid that will prevent NTDs.

In addition to preventing many NTDs, food fortification has provided valuable information about how much folic acid is needed to prevent these birth defects. The 2 major clinical trials of folic acid supplementation conducted in the 1990s had used doses twice¹² and 10 times¹ the recommended dietary allowance (RDA), but the USPHS thought that those doses were too high to recommend for the general population. The USPHS selected a dose of 400 µg (the RDA) as the target dose because that was the amount in typical multivitamins, and multivitamins had shown a protective association in case-control studies. Fortification is estimated to provide 163 µg per day on average to the target population.¹³ If this dose were sufficient to prevent folate-related NTDs, it would demonstrate that prevention is possible without exposing the general population to high doses of folic acid. As the USPSTF points out,⁵ models using blood folate concentrations to estimate the optimal dose show that 400 µg per day may be needed.¹⁴ Clinical data, however, show large reductions in NTD rates in countries that fortify foods at the same level as the United States.¹⁰

Two studies have examined whether taking supplements has been associated with any additional protection in the US population in the fortification era.^{15,16} It is noteworthy that both have shown that women who had infants with NTDs were no less likely to take supplements than women who had unaffected infants. These results suggest that food fortification at the current modest level is preventing most, if not all, folate-related NTDs. The 400 to 800 µg per day recommended by the USPSTF may be more than is needed to prevent NTDs. If the amount of folic acid currently being added to food is sufficient, concerns regarding excess exposure in the nontarget population in countries where food is fortified with folic acid might be reduced.

Should the USPSTF recommendation be rejected because fortified food is already providing sufficient folic acid to prevent NTDs? No. Too little is known about how folic acid prevents

NTDs. For example, it is not known whether the tissue stores of folate in the developing embryo or the availability of folate in the serum during the all-important few days of neural tube closure is most important. Habitual use of folic acid supplements is a more reliable method of ensuring adequate levels than diet. In theory, a woman might not consume sufficient enriched cereal grains during the critical period of approximately 1 week when the neural tube is closing. Exactly when folate must be available also is not known. In addition, some popular diets, such as low-carbohydrate or gluten-free, may reduce exposure to grains, limiting folic acid intake.

The USPSTF recommendation that all women of childbearing age take folic acid supplements is a prudent one. Ideally, it will educate all women who are planning or capable of pregnancy to follow this recommendation and thereby reduce the risk of these severe birth defects in their infants.

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REFERENCES

1. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991;338 (8760):131–137. [PubMed: 1677062]
2. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep* 1992;41(RR-14):1–7.
3. Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008–2011. *N Engl J Med* 2016;374(9):843–852. [PubMed: 26962904]
4. US Preventive Services Task Force. Folic acid for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;150(9):626–631. [PubMed: 19414842]
5. US Preventive Services Task Force. Folic acid supplementation for the prevention of neural tube defects: US Preventive Services Task Force Recommendation Statement. *JAMA*. doi:10.1001/jama.2016.19438
6. Green-Raleigh K, Carter H, Mulinare J, Prue C, Petrini J Trends in folic Acid awareness and behavior in the United States: the Gallup Organization for the March of Dimes Foundation surveys, 1995–2005. *Matern Child Health J* 2006; 10(5)(suppl):S177–S182. [PubMed: 16823638]
7. Khoshnood B, Loane M, de Walle H, et al. Long term trends in prevalence of neural tube defects in Europe: population based study. *BMJ*. 2015;351: h5949. [PubMed: 26601850]
8. US Department of Health and Human Services. Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid. *Fed Regist* 1996;61(44):8781–8797.
9. Food Fortification Initiative. Global progress. Food Fortification Initiative website. http://www.ffinetwork.org/global_progress/index.php.2016 Accessed April 1, 2016.
10. Castillo-Lancellotti C, Tur JA, Uauy R. Impact of folic acid fortification of flour on neural tube defects: a systematic review. *Public Health Nutr*. 2013;16(5):901–911. [PubMed: 22850218]
11. Mills JL, Dimopoulos A. Folic acid fortification for Europe? *BMJ*. 2015;351:h6198. [PubMed: 26602789]
12. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327(26):1832–1835. [PubMed: 1307234]
13. Tinker SC, Cogswell ME, Devine O, Berry RJ. Folic acid intake among U.S. women aged 15–44 years, National Health and Nutrition Examination Survey, 2003–2006. *Am J Prev Med* 2010;38(5): 534–542. [PubMed: 20347553]

14. Daly S, Mills JL, Molloy AM, et al. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. *Lancet*. 1997;350 (9092):1666–1669. [PubMed: 9400511]
15. Ahrens K, Yazdy MM, Mitchell AA, Werler MM. Folic acid intake and spina bifida in the era of dietary folic acid fortification. *Epidemiology*. 2011; 22(5):731–73. [PubMed: 21659881]
16. Mosley BS, Cleves MA, Siega-Riz AM, et al.; National Birth Defects Prevention Study. Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States. *Am J Epidemiol* 2009;169 (1):9–17. [PubMed: 18953063]