EDITORIAL

Folic Acid for the Prevention of Neural Tube Defects
The US Preventive Services Task Force Statement on Folic Acid Supplementation in the Era of Mandatory Folic Acid Fortification

Laura E. Mitchell, PhD

In the current issue of *JAMA*, The US Preventive Services Task Force (USPSTF) has published an update to its 2009 recommendation statement on the use of folic acid supplementation to prevent neural tube defects.[1] The updated statement, informed by a systematic review of relevant information,[2] remains unchanged from the 2009 recommendation. Specifically, the USPSTF continues to recommend that all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid to reduce their risk of having a pregnancy affected by a neural tube defect. This recommendation applies to all women who are capable of becoming pregnant with the exception of women who have a high risk of a neural tube defect–affected pregnancy because they have a history of an affected pregnancy or another strong risk factor (eg, use of certain antiseizure medications). These women may be advised to take higher doses of folic acid. Like the 2009 recommendation, the current recommendation received a USPSTF grade of A. This grade indicates that there is a high certainty that folic acid supplementation is an effective means of primary prevention for neural tube defects. In addition, the A grade indicates that clinicians should advise women who are capable of becoming pregnant about the benefits of taking a daily folic acid supplement.

Related articles at jama.com

The history leading to the USPSTF recommendation on folic acid dates back to the 1960s, when it was noted that women who gave birth to a child with a neural tube defect were more likely than women with an unaffected child to have evidence of impaired folate status. By the early 1990s, the link between maternal use of folic acid and the risk of neural tube defects (primarily anencephaly and spina bifida) in offspring was strong: the evidence included results from 2 large randomized clinical trials as well as the findings from additional trials and observational studies.[3] Based on this evidence, the US Public Health Service issued recommendations about the use of folic acid supplements for women with a prior neural tube defect–affected pregnancy (1991)[4] and for women without such a history (1992).[5] In addition, the US Centers for Disease Control and Prevention (CDC) and the March of Dimes initiated efforts that ultimately led the US Food and Drug Administration (FDA) to mandate folic acid fortification of enriched grain products (140 µg folic acid/100 g of cereal grain product).[6] In the United States, mandatory folic acid fortification was initiated in January 1998 and was followed by a 35% decline in the prevalence of neural tube defects.[7]

While the USPSTF recommendation regarding folic acid supplementation has not changed since 2009, the Task Force did consider new information obtained after mandatory folic acid fortification of grain products in the United States. This included the results from 2 case-control studies that evaluated the association between maternal use of folic acid–containing supplements and the risk of neural tube defects in offspring conceived after mandatory fortification.[8,9] In contrast to the majority of studies conducted prior to fortification, neither of these studies found an association between maternal use of folic acid supplements immediately prior to and during early pregnancy and the risk of neural tube defects. These findings may indicate that folic acid fortification is preventing nearly all cases of folic acid–related neural tube defects. However, as both studies relied on maternal recall of folic acid supplementation during pregnancy, these findings may also reflect bias resulting from errors in maternal recall. Moreover, although both studies were relatively large, they might have had low power to detect a true effect of folic acid supplementation against the backdrop of a fortified food supply.

Given the strong evidence for a protective effect of folic acid supplementation in unfortified populations and the lack of definitive evidence against such an effect in fortified populations, the current USPSTF recommendation is prudent. Moreover, further support for this recommendation is provided by a study of folate status in reproductive-age women in the United States following fortification.[10] Specifically, data from the National Health and Nutrition Examination Survey 2007 to 2012[10] indicate that the red blood cell folate levels of nearly one-quarter of all reproductive-age women are suboptimal for the prevention of neural tube defects. Furthermore, compared with women who use folic acid supplements, those who do not are approximately 3 times more likely to have suboptimal folate levels.[10] Hence, even in the era of mandatory folic acid fortification of the food supply, taking a daily supplement remains an important strategy for women to optimize their intake of folic acid.

While the USPSTF recommendation is sound, implementation of the recommendation has been a challenge—similar recommendations have been in place since 1992, yet less than

one-third of reproductive-age US women take a daily supplement containing folic acid.[10-12] Moreover, in some subgroups, the proportion of women who take a daily supplement is even lower (eg, Hispanic women, about 23%; women with unintended pregnancies, about 16%).[12] While messages targeted to such subgroups have been developed by the CDC and others, and the FDA has recently approved the voluntary fortification of corn masa flour in an effort to increase folic acid intake,[13] particularly among Hispanic women, further efforts to address disparities in the use of folic acid supplements are warranted. However, even within the subgroups of women who have the highest rates of supplementation, the proportion of women who follow the recommendation is relatively low. For example, among women with intended pregnancies, less than half took a daily folic acid supplement in the month prior to pregnancy.[12] Hence, there is considerable room for improvement in the use of folic acid supplements across the population of reproductive-age women.

The major challenges to increasing the proportion of women who take a daily folic acid supplement are not new: behavioral change is hard; the reproductive period is long; and messages about the health of a hypothetical future child often do not resonate with the target audience. However, there have been changes since the initial folic acid awareness campaigns of the 1990s that provide new opportunities to address these challenges. For example, wearable devices and smartphone-based self-trackers provide new approaches for disseminating information on folic acid supplementation (eg, as a component of menstruation and ovulation trackers) as well as for self-monitoring of supplement use (eg, using pill reminders and medication trackers) and are well suited to the development of messages and approaches that are targeted to specific subgroups of women. In addition, a national effort to promote preconception health, the National Preconception Health and Healthcare Initiative,[14] has the potential to drive broad system changes that will increase women's awareness of and receptiveness to health-related information, including the USPSTF recommendation on folic acid supplements.

While identification of the causal link between folic acid and neural tube defects and the subsequent reduction in the prevalence of these conditions via folic acid fortification are remarkable public health successes, the current USPSTF recommendation provides an important reminder that we have yet to achieve the full benefit of these successes. Consequently, the current recommendation statement should serve as a catalyst for renewed efforts to develop and deliver folic acid messages that will translate into further reductions in the population prevalence of neural tube defects.

ARTICLE INFORMATION

Author Affiliation: Department of Epidemiology, Human Genetics and Environmental Sciences and Human Genetics Center, UTHealth School of Public Health, Houston, Texas.

Corresponding Author: Laura E. Mitchell, PhD, UTHealth School of Public Health, 1200 Pressler St, Houston, TX 77030 (Laura.E.Mitchell@uth.tmc.edu).

Published Online: January 10, 2017. doi:10.1001/jamapediatrics.2016.4983

Conflict of Interest Disclosures: None reported.

REFERENCES

1. 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

2. Viswanathan M, Treiman KA, Kish-Doto J, Middleton JC, Coker-Schwimmer EJL, Nicholson WK. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. doi:10.1001/jama.2016.19193

3. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification: its history, effect, concerns, and future directions. *Nutrients*. 2011;3(3):370-384.

4. Centers for Disease Control (CDC). Use of folic acid for prevention of spina bifida and other neural tube defects—1983-1991. *MMWR Morb Mortal Wkly Rep*. 1991;40(30):513-516.

5. Centers for Disease Control and Prevention. 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.

6. US Food and Drug Administration. Food standards: amendment of standards of identity or enriched grain products to require addition of folic acid. https://www.gpo.gov/fdsys/pkg/FR-1996-03-05/pdf/96-5014.pdf. Accessed December 22, 2016.

7. Williams J, Mai CT, Mulinare J, et al; Centers for Disease Control and Prevention. Updated estimates of neural tube defects prevented by mandatory folic acid fortification—United States, 1995-2011. *MMWR Morb Mortal Wkly Rep*. 2015;64(1):1-5.

8. 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):731-737.

9. 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.

10. Tinker SC, Hamner HC, Qi YP, Crider KS. U.S. women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red blood cell folate concentrations, National Health and Nutrition Examination Survey 2007 to 2012. *Birth Defects Res A Clin Mol Teratol*. 2015;103(6):517-526.

11. Khodr ZG, Lupo PJ, Agopian AJ, et al. Preconceptional folic acid-containing supplement use in the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol*. 2014;100(6):472-482.

12. Masho SW, Bassyouni A, Cha S. Pre-pregnancy obesity and non-adherence to multivitamin use: findings from the National Pregnancy Risk Assessment Monitoring System (2009-2011). *BMC Pregnancy Childbirth*. 2016;16(1):210.

13. Food and Drug Administration, HHS. Food additives permitted for direct addition to food for human consumption; folic acid: final rule. *Fed Regist*. 2016;81(73):22176-22183.

14. Johnson K, Posner SF, Biermann J, et al; CDC/ATSDR Preconception Care Work Group; Select Panel on Preconception Care. Recommendations to improve preconception health and health care—United States: a report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep*. 2006;55(RR-6):1-23.