Genetics inMedicine | ADDENDUM

Focused Revision: Policy statement on folic acid and neural tube defects

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This document was reaffirmed by the American College of Medical Genetics and Genomics (ACMG) Board of Directors as of 12 April 2021 noting that the original document does not meet the criteria for an evidence-based practice guideline by the ACMG (2014), and is now reclassified as a Clinical Practice Resource. This addendum is a Focused Revision of the original document.

Since the publication of the original article in 2011, a nonsystematic review of the literature for updated information on the role of folic acid supplementation in decreasing the prevalence of neural tube defects (NTDs) was done through PubMed and websites of various national health-care organizations, e.g., Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities (NCBDDD), and the US Preventive Services Task Force (USPSTF).

Since 2011, multiple medical and public health organizations have reiterated the recommendation of universal folic acid prophylaxis of 400 µg (0.4 mg) daily in all women of child-bearing age to prevent the incidence of NTDs in fetuses.[1–4] This folic acid dose should supplement the consumption of a folate-rich diet including enriched cereal grains.

Studies have shown risk differences in populations of various racial and ethnic backgrounds, as well as in various geographical locations.[5] Shanxi Province in China has been documented to have the highest rate of NTDs in the world. While the Chinese government's implementation of NTD prevention programs by food fortification with micronutrients including folic acid decreased the NTD incidence significantly ($P < 0.05$), study of this geographical area highlighted the significant role of geographical and environmental risk factors in the higher NTD incidence, which might not be addressed with diet and vitamin supplementation alone.[6]

In 2010, the NCBDDD and the CDC launched an initiative with a global network of partners, including the World Health Organization, named Birth Defects COUNT (Countries and Organizations United for Neural Tube Defects Prevention).[7] It aims to reduce the death and lifelong disability due to NTDs by increasing the intake of folic acid to at least 400 µg (0.4 mg) per day in all reproductive-age women.

In the United States, some studies have found the highest risk for NTDs in Hispanic women, while others have not found such an association.[5,8] In 2016, the US Food and Drug Administration approved voluntary folic acid fortification of corn masa flour to address this disparity and increase total daily folic acid intake in this subpopulation.[9] This is estimated to prevent 40 additional cases of NTDs in Hispanic infants every year.[10]

As approximately 50% of pregnancies in the United States are unplanned, universal prophylaxis with daily folic acid of 400 µg (0.4 mg) is recommended for general reproductive-age women, in addition to a folate-rich diet. In women contemplating pregnancy, the intake should commence at least one month before conception and continue till 12 weeks gestation for maximal protection.[1–3] Although vitamin supplementation beyond 12 weeks is not required for neural tube protection, continuation of 400 µg (0.4 mg) folic acid as a standard component of many prenatal vitamins is recommended throughout the rest of the pregnancy to meet the fetal growth and developmental needs.[11,12]

For high-risk women, the recommendation of a higher folic acid dose supplementation of 4,000 µg (4 mg) daily has been reiterated by various US organizations.[1–3] This high dose should be commenced at least three months prior to conception and continued until 12 weeks gestation till completion of major organ development, after which the dose can be reduced to 400 µg (0.4 mg) daily.[13] This

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decreases the likelihood of any potential health consequences of long-term ingestion of high doses of folic acid, e.g., masking vitamin B12 deficiency–related neurological symptoms.[14]

Continued experience has shown that even with adequate folate supplementation, not all cases of isolated NTDs can be prevented due to their multifactorial etiology.[15,16]

In 2017, a systematic review by the USPSTF reaffirmed the adequacy of current folic acid supplementation guidelines with recommended daily supplementation of 400–800 µg (0.4 to 0.8 mg) in all women at average risk. The task force acknowledged that it is difficult for most women to consume the recommended daily folic acid from food alone in spite of access to fortified food. However, in their review of case–control studies conducted after implementation of food fortification laws, the benefit of additional folic acid supplementation was noted to be smaller than that afforded by food fortification.[3,17] The USPSTF stated that the reflected reduced magnitude of protective effect of folic acid supplementation after food fortification could be attributed to study design.[3] They concluded with high certainty that the net benefit of folic acid supplementation is substantial with inadequate evidence for any potential harm to the mother or baby.[1] The USPSTF has therefore reaffirmed its 2009 recommendation of daily folic acid supplementation at a dose of 400–800 µg (0.4–0.8 mg) daily in all reproductive-age women.

A Cochrane meta-analysis showed that higher doses of folate supplementation (>400 µg or >0.4 mg) with or without additional vitamins and minerals do not have any effect on the prevalence or recurrence of NTDs. According to the meta-analysis, the same or higher dose also has no potential protective role in other birth defects including, but not limited to, cleft lip/palate, congenital heart defects, miscarriages, limb reduction defects, urinary tract defects, or congenital hydrocephalus.[18] Although findings are based on low-quality data, the Society of Obstetricians and Gynaecologists of Canada recommends 1 mg folic acid per day for women who have a personal history of the abovementioned conditions. This dose is also recommended if they have a partner, prior offspring, or first or second degree relatives with the same.[13]

Although some studies have reported a protective role of folic acid in fetal growth restriction and preterm birth, the findings have not been conclusive enough to warrant any change in the dose of prophylactic folic acid supplementation.[19,20]

While folic acid's preventive role is well established, avoidance of drugs that increase the risk of fetal NTDs, like the methotrexate or antiseizure medications (e.g., valproic acid or carbamazepine), should be considered during pregnancy, if clinically safe. Some other micronutrients that have been investigated to have a preventive role in fetal NTDs include thiamine, betaine, riboflavin, vitamin B6, vitamin C, vitamin E, niacin, iron, retinol, vitamin A, and choline.[21,22] Recently, periconceptional myo-inositol supplementation has been shown to have a role in ameliorating the risk of fetal NTDs, especially in folate-resistant cases.[23] More research with the above micronutrients is needed before a scientific recommendation can be made.

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS RECOMMENDATIONS

1. Daily folic acid intake of 400 µg (0.4 mg) is recommended in all women of child-bearing age. In women planning a pregnancy, the intake is recommended to start at least 4 weeks prior to planned conception. This supplementation is advised in addition to consumption of folic acid fortified food from the preconception period at least through the first trimester.
2. High-risk women are recommended to take a higher dose, 4,000 µg (4 mg) of daily folic acid supplementation at least 12 weeks prior to conception, with continuation of reduced folic acid supplementation dose of 400 µg (0.4 mg) after completion of 12 weeks gestation. Some criteria in defining high-risk status include (but are not limited to) personal, family, or prior pregnancy history of neural tube defects; type 1 diabetes mellitus; or exposure to high-risk medications during early pregnancy.
3. In spite of patient compliance with supplementation, some fetal neural tube defects are of multifactorial or monogenic etiology, and cannot be completely prevented.

COMPETING INTERESTS

The authors declare no competing interests.

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