Folic acid and prevention of neural tube defects

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ABSTRACT

QUESTION Now that flour and pasta have been fortified with folic acid in Canada, do I still need to recommend folic acid supplements to my patients who are of child-bearing age? If I should recommend supplements, when should I recommend them, and what is an appropriate dose?

ANSWER Non-pregnant women should consume 400 µg of folic acid daily, and pregnant women should consume 600 µg of folic acid daily. Mean intakes of folate in Canada before fortification were around 200 µg/d or less. Fortification increased intake of folic acid by up to 100 µg/d. You should discuss the importance of folic acid with your patients who are planning pregnancy; it is recommended that a folic acid supplement or prenatal multivitamin containing at least 400 µg of folic acid be consumed daily. The upper limit for folic acid is 1 mg/d. Women in intermediate- to high-risk categories for neural tube defects, such as a previous neural tube defect–affected pregnancy, should take 4 to 5 mg of folic acid daily.

RÉSUMÉ

QUESTION Maintenant que la farine et les pâtes sont enrichies d'acide folique au Canada, dois-je toujours recommander un supplément d'acide folique à mes patientes en âge de procréer? Dans l'affirmative, quand devrais-je le recommander et quelle est la dose appropriée?

RÉPONSE Les femmes qui ne sont pas enceintes devraient prendre 400 µg d'acide folique par jour et les femmes enceintes, 600 µg par jour. L'apport moyen en acide folique au Canada avant qu'on enrichisse les aliments était de 200 µg/j ou moins. L'enrichissement a fait grimper cet apport de 100 µg/j environ. Vous devriez discuter de l'importance de l'acide folique avec vos patientes qui prévoient une grossesse; on recommande un supplément d'acide folique ou une multivitamine prénatale contenant au moins 400 µg chaque jour. La dose maximale d'acide folique est de 1 mg/j. Les femmes appartenant à la catégorie de risque modéré à élevé d'anomalies du tube neural, comme une grossesse antérieure où il y avait anomalie du tube neural, devraient prendre de 4 à 5 mg d'acide folique par jour.

Maternal folate status is involved in the pathogenesis of neural tube defects (NTDs), and although the exact mechanism is not clear, a nutritional or genetic defect in homocysteine metabolism via methionine synthase appears likely. Women who previously had infants with NTDs were found to have had higher plasma homocysteine levels than women who had normal offspring.[1,2]

Higher homocysteine levels can be indicative of the presence of a metabolic defect that increases risk of NTDs or other congenital defects. The rapidly dividing cells of the neural tube can be particularly sensitive to folate because of its importance to methyl group metabolism in nucleic acid and amino acid biosynthesis.[3]

Certainly, the scientific evidence that folic acid taken around the time of conception prevents many NTDs has been very strong.[4] In Canada starting in January 1998, flour and pasta were fortified with folic acid to help prevent NTDs, and results have been very encouraging.[5] In Europe, recommendations to increase folic acid through voluntary supplementation did not reduce the incidence of NTDs; however, food fortification had not been implemented.[6] Interestingly enough, however, when physicians took an active role in promoting folic acid supplementation, folic acid intake increased. Women who received folic acid counseling, a 30-day supply of folic acid tablets, and a reminder telephone call increased their folic acid intake by 68%, compared with 20% of controls who received only a pamphlet on folic acid.[7]

Periconceptional use of folic acid has been shown to reduce the incidence of non-NTD birth defects, such as cleft palates, upper limb reduction deficits, and genitourinary defects.[8] Others have also observed a link between folic acid and congenital heart defects, urinary tract anomalies, orofacial clefts, limb defects, and pyloric stenosis.[9]

Recommendations on folic acid supplementation

Before fortification, mean intakes of folate in Canada were less than 200 µg/d, though folate content in foods generally has been underestimated. United States data placed the average folate intake at about 250 µg/d.[10] Fortification increases dietary consumption by up to

100 µg/d or about 25% of the recommended daily allowance.[11] During pregnancy, folic acid should be increased to 600 µg/d.[10] Many pregnancies are unplanned, and women often do not know that they are pregnant until the crucial first 4 to 8 weeks of pregnancy. This is the time during which neural tube development occurs, hence the importance of ensuring adequate folic acid intake. Therefore, to achieve the greatest benefit in NTD risk reduction, women of child-bearing age should be consuming total folic acid intakes of at least 400 µg, and probably 600 µg, daily. A daily supplement of 400 µg of folic acid should remain an important component of NTD prevention.[12]

Some individuals might have a greater requirement for folic acid based upon their ethnic background. One study determined that in the Welsh population, about 12% of people have the TT genotype of the methylenetetrahydrofolate reductase 677C→T mutation. Therefore, the study's authors suggested that a folate-enrichment policy be formulated to help these individuals achieve intakes between 400 and 600 µg/d.[13] In another study, women with the TT genotype appeared to benefit the most from folic acid supplementation intended to lower plasma total homocysteine.[14] In Canada, women of First Nations origin had a higher risk of having an NTD-affected pregnancy than did white women. Although obesity and type 2 diabetes could have been the risk factors for these NTDs, other mechanisms that might be related to folate status should be explored within this population.[15]

Overall, the goal should be to increase red blood cell folate concentrations to greater than 905 nmol/L, a level associated with a low risk of having a child with an NTD. In women, a 400-µg daily dose of folic acid raised the red blood cell concentration to 1053 nmol/L from a baseline of 615 nmol/L after 12 weeks. This study also showed that a once-a-week folic acid supplement (2800 µg) also raised red blood cell folate concentrations, but not as effectively as a daily supplement.[16] For women who have an intermediate to high risk of having an NTD-affected pregnancy, the Society of Obstetricians and Gynaecologists of Canada *recommends a daily intake of high-dose (4 to 5 mg) folic acid supplementation.[17] Some studies have shown that lower doses of folic acid (300 µg or less) have the potential to lower total homocysteine concentrations, especially in those individuals who are in the higher range of homocysteine values.[18,19] It is most important, however, that women of child-bearing age achieve adequate folate status through consumption of vegetables, fruit, and fortified grain products, and take folic acid in supplement form as a risk-reduction strategy.

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Competing interests

Dr Aldoori *is employed by and* **Dr Ryan-Harshman** *received a grant to co-author this article from Wyeth Consumer Healthcare Inc.*

**New, more extensive clinical practice guidelines were published in the December 2007 issue of the* Journal of Obstetrics and Gynaecology Canada *(2007;29[12]:1003-13).*

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