Folic acid

The right dose

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ABSTRACT

QUESTION The new Motherisk Guidelines suggest 5 mg/d of folic acid. Why was the dose increased? What is the time frame for taking such a dose?

ANSWER Recent data from Ontario reveal that 40% of women of reproductive age still do not achieve therapeutic systemic levels of folate needed to prevent neural tube defects. Compliance is less than optimal among women using prenatal vitamins, rendering many women unprotected against neural tube defects. Taking a higher dose of folate will allow achievement of protective folate levels, even with partial compliance. Five mg of folate should be used daily several months before conception until the end of the first trimester.

RÉSUMÉ

QUESTION Les nouvelles lignes directrices de Motherisk suggèrent une dose de 5 mg/j d'acide folique. Pourquoi a-t-on augmenté la dose? Pendant combien de temps faut-il prendre une telle dose?

RÉPONSE De récentes données en provenance de l'Ontario révèlent que 40% des femmes en âge de procréer n'atteignent toujours pas les taux systémiques thérapeutiques d'acide folique nécessaires pour prévenir les anomalies du tube neural. L'observance du traitement est sous-optimale chez les femmes qui utilisent des vitamines prénatales, ce qui laisse beaucoup de femmes sans protection contre les anomalies du tube neural. En prenant une plus forte dose d'acide folique, elles peuvent atteindre les taux nécessaires pour la prévention, même si elles ne respectent que partiellement la posologie. Il faut prendre 5 mg d'acide folique pendant quelques mois avant la conception et jusqu'à la fin du premier trimestre.

Neural tube defects (NTDs) are malformations of the cranium, spine, and nervous system; types of NTDs include anencephaly, spina bifida, encephalocele, and meningocele. Neural tube defects are a major cause of mortality in newborns and have been estimated to affect 0.5 to 8 per 1000 live births. Health Canada has estimated that 195 Canadian infants are born each year with NTDs. Overall, NTDs affect approximately 300 000 infants worldwide.

Epidemiological studies that associate folate supplementation with a decreased risk of NTDs date back to the 1960s. The most definitive research addressing the benefits of folic acid supplementation in decreasing the risk of NTDs was the multicentre, randomized, double-blind trial by the Medical Research Council in the United Kingdom.[1] The aim of this trial was to evaluate the efficacy of 4-mg doses of folic acid in preventing recurrent NTDs in women who had previously delivered children with NTDs. The trial showed that women randomized to take folic acid supplementation had a 1.0% chance of having children with NTDs (relative risk [RR] 0.28, 95% confidence interval [CI] 0.12 to 0.71), but women in the unsupplemented group did not show a decrease in the risk of NTDs (3.49%) (RR 0.8, 95% CI 0.37 to 1.72).[1,2] Overall, supplementation with folic acid reduced the rate of recurrence of NTDs by 72% (6/593 with folate supplements vs 21/602 without).[1]

A second key trial evaluating folic acid–fortified multivitamin supplementation during pregnancy was a double-blind, randomized controlled trial, in which women were randomized to take a multivitamin supplement containing 0.8 mg of folic acid or a multivitamin containing trace-element supplementation.[2] Five thousand women were randomized in each group; no NTDs were observed in babies from the folic acid–fortified group, whereas 6 NTDs were found in those from the trace-element group.

A recent meta-analysis observed an odds ratio (OR) of 0.67 (95% CI 0.58 to 0.77) in case-control studies and an OR 0.52 (95% CI 0.39 to 0.69) in cohort and randomized controlled studies.[3] An OR of 0.67 means 0.33 (or 33%) protective effect; an OR of 0.52 means 0.48 (or 48%) protective effect.[3]

A study investigating the relationship between serum and red blood folate concentrations and the risk of NTDs found an inverse relationship between maternal red blood cell folate and the risk of NTD.[4] Daly et al showed that women receiving less than 150 µg and

more than 400 µg of folic acid had a 6.6/1000 and 0.8/1000 chance of having children with NTDs, respectively. Supplementation at doses of 100 µg, 200 µg, and 400 µg of folic acid resulted in a 22%, 41%, and 47% decreased risk of NTDs, respectively.[5]

Optimal dose of folic acid supplementation

For almost 20 years, the recommended daily dose of folate supplementation has been 0.4 mg/d. In fact, prenatal multivitamins invariably contain 0.8 to 1.1 mg of folic acid, and this had led to the assumption that daily supplementation with this dose is sufficient to prevent NTDs. However, in 2001, Wald et al systematically reviewed all reports of the correlation between ingested dose of folate and resultant serum concentrations.[6] Using the data by Daly et al,[5] who correlated maternal serum folate levels with the risk of NTDs, Wald et al concluded that the current recommended daily dose of folate will render only partial protection against NTDs. According to Wald et al's analysis, 5 mg/d of folate would be necessary to render 90% protection within the populations.[6] Their analysis has been recently corroborated by our findings that in 2005 and 2006, 40% of women in Ontario did not achieve the protective 900 nmol/L red blood cell folate, despite flour fortification and the fact that more than half of pregnant women supplemented with prenatal multivitamins.[7]

Potential risks

Before recommending prenatal supplementation with higher doses of folic acid, one needs to consider potential health risks of such an increase.

It has been proposed that higher levels of folate can mask pernicious anemia due to B12 deficiency. Similar concerns surrounded the original North American flour folate fortification program in 1998, but were not shown following the fortification. Several recent studies have failed to show such risks.[8] A recent US study suggested an association between high folate levels in older Americans and a risk of cognitive impairment.[9] However, cognitive impairment is not a component of pernicious anemia, and in that study there was no increased risk for neuritis, which is a typical finding of pernicious anemia. One has to remember that the risk for the pernicious anemia is different if the whole population consumes flour with higher levels of folate, as opposed to giving 5 mg/d to pregnant women for a limited time. In fact, direct measurements of B12, or higher supplementation of B12, can further allay these concerns.

If women do not comply with the recommendation to take the currently available folate-cotaining preparations, it is reasonable to question whether or not they would take the preparations containing 5 mg of folate daily. In a recent controlled trial of prenatal vitamin supplements for women who discontinued or had not started using prenatal vitamins, their compliance with 2 different brands of prenatal vitamins averaged 58% and ranged from 0 to 100%, despite the participation of self-selected, motivated women.[10] Pharmacologically, administration of 5 mg of folate daily in women who have a lower compliance with taking medication should provide many more women with protective levels of folate.

Although laboratory studies have suggested that folic acid might increase the risk of certain cancers, population-based studies have repeatedly shown folic acid use to be associated with a 20% to 30% decline in incidence (**Table 1**[8]). Scientists therefore refer to the potential dual effects of folate on cancer risk, with increased risk for individuals with a history of or predisposition to cancer.[11] There is no question that an increased risk of cancer associated with folate use, even if it exists, is a result of long-term exposure to folate over many years, and not to several months of dosing during pregnancy.

Table 1. Associations between folate status and risk of selected cancers

TYPE OF CANCER	ASSOCIATION OF FOLATE AND RISK
Breast	• Meta-analysis shows decrease in cancer risk with high folate status • Majority of case-control studies show reduction in risk (30% to 35%) at the highest dietary intake of folate • Might increase risk postmenopausal (statistically non-significant) • A non-significant trend for increase in breast cancer mortality when fortified with 5 mg/d
Colorectal	• Inverse relationship between folate status and risk of colorectal cancer in healthy people • Potential increased risk of adenoma
Pancreatic	• Decreased risk with higher folate status
Ovarian	• Statistically significant decrease in the serous subtype • Prospective prevention (non-significant trend)
Bladder	• Statistically significant lower folate in cancer subjects as compared with controls
Carcinoma of head and neck	• Protective effect
Stomach	• No effect
Esophageal and gastric	• Protective effect in case-control studies
Non-Hodgkin lymphoma	• No correlation with folate status
Cervical	• Folate fortification not associated with the degree or pattern of global DNA methylation in cells involved in cervical carcinogenesis

Data from Koren and Goh.[8]

Incidentally, a systematic review that assessed the association between folate status and twinning found possible but non-significant evidence of periconceptional folate intake and twinning.[8]

Conclusion

Unless prescribing clinicians can ensure that pregnant women will be appropriately compliant in using prenatal vitamin supplements containing 0.8 to 1.1 mg of folate, they should consider prenatal vitamin supplements containing 5 mg of folate daily.[12] Five mg of folate should be used several months before conception until the end of the first trimester of pregnancy.

Competing interests

Motherisk received financial support from Duchesnay Inc and Wyeth Inc, manufacturers of prenatal vitamins. **Dr Koren** has served as a consultant for Duchesnay Inc.

References

1. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet* 1991;338(8760):131-7.
2. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327(26):1832-5.
3. Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis. *J Obstet Gynaecol Can* 2006;28(8):680-9.
4. Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects. Implications for prevention. *JAMA* 1995;274(21):1698-702.
5. Daly S, Mills JL, Molloy AM, Conley M, Lee YJ, Kirke PN, et al. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. *Lancet* 1997;350(9298):1666-9.
6. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. *Lancet* 2001;358(9298):2069-73.
7. Bar-Oz B, Koren G, Nguyen P, Kapur B. Folate fortification and supplementation—are we there yet? *Reprod Toxicol* 2008;25(4):408-12. Epub 2008 May 3.
8. Koren G, Goh I. Increasing folate supplementation for selected groups of Canadian women. *J Obstet Gynaecol Can* 2007;29(12):992-6.
9. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. *Am J Clin Nutr* 2007;85(1):193-200.
10. Nguyen P, Einarson A, Nava-Ocampo A, Koren G. Improving the tolerability of prenatal multivitamins for prengant women: reduced tablet size. *Can J Clin Pharmacol* 2007;14:e176.
11. Kim YI. Does a high folate intake increase the risk of breast cancer? *Nutr Rev* 2006;64(10 Pt 1):468-75.
12. Wilson RD, Johnson JA, Wyatt P, Allen V, Gagnon A, Langlois S, et al. Preconceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can* 2007;29(12):1003-26. Erratum in: *J Obstet Gynaecol Can* 2007;30(3):193.

MOTHERISK

Motherisk questions are prepared by the **Motherisk Team** at the Hospital for Sick Children in Toronto, Ont. **Ms Goh** and **Dr Klieger** are members and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

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