MOTHERISK ROUNDS

Increasing Folate Supplementation for Selected Groups of Canadian Women

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Abstract

After review of current evidence related to the potential risks and benefits of folic acid supplementation, we conclude that unless clinicians can be assured that pregnant women will reliably use prenatal vitamin supplements containing 0.8–1.1 mg of folate, the prenatal vitamin supplements should be combined with 5 mg of folate.

Résumé

À la suite de l'analyse des données actuelles quant aux risques et aux avantages potentiels de la supplémentation en acide folique, nous en sommes venus à la conclusion suivante : à moins que les cliniciens puissent être assurés que les femmes enceintes utiliseront de façon fiable des suppléments vitaminiques prénatals contenant 0,8–1,1 mg de folate, les suppléments vitaminiques prénatals devraient être utilisés conjointement avec 5 mg de folate

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BACKGROUND

Folic acid is essential for growth and differentiation, repair, and host defence[1] and hence it is essential for fetal development. The term "folic acid" generally refers to the fully oxidized form of the chemical compound, which is not naturally available in foods. The term "folate" refers to the group of compounds that have the same vitamin activity, encompassing both folic acid and naturally occurring folates. Folates are composed of a pteridine ring and p-aminobenzoic acid, and may contain one to six glutamate molecules that are joined by peptide linkages.[2,3] Natural folates are found in the form of polyglutamates. These are relatively heat labile molecules that may be destroyed by storage, processing, and cooking and that are not readily absorbed by the body.[1]

Key Words: Folic acid, pregnancy, multivitamin

Folate monoglutamates are transported to the fetus by folate receptors that are highly expressed in the embryo and fetus, especially in the neural folds prior to the closure of the neural tube.[4] During embryogenesis and fetal growth, nucleic acid and protein synthesis rely on a supply of folate, and therefore the requirement for maternal folate increases during this period of cell formation.[2] A deficient folate supply or any problem in its metabolism may result in impaired cell formation and tissue growth.[5] Consequently, nucleic acids will not be synthesized and cells will be unable to manufacture enough DNA for mitosis, resulting in abnormal cell division.[2] Proteins, lipids, and myelin will also not be methylated because of the inhibition of the methylation cycle. Since cells are rapidly dividing during the fetal period, they are most susceptible to irregularities in DNA production. Congenital birth defects affect up to 5% of newborns[6]; however, only 2% to 3% are recognized at birth.

ASSOCIATED CONDITIONS

Folic Acid and Neural Tube Defects

NTDs comprise malformations of the cranium, spine, and nervous system, including anencephaly, spina bifida, encephalocele, and meningocele. These malformations are a major cause of mortality in newborns, second only to congenital heart defects. They have been estimated to affect 0.5 to 8 newborns per 1000 live births.[7] Health Canada has estimated that 195 Canadian infants are born each year with NTDs,[8] and it has been estimated that NTDs annually affect 300 000 infants worldwide.[9] Epidemiological studies associating folate supplementation with a decreasing incidence of NTDs date back to the 1960s.[10,11] The most definitive research addressing the benefits of folic acid supplementation in decreasing the risk of NTDs was a

multicentre randomized double-blind trial instigated by the United Kingdom Medical Research Council.[12] The aim of this trial was to evaluate the efficacy of folic acid 4 mg daily in preventing an NTD in subsequent offspring of women who had previously delivered a child with an NTD. The trial took place in seven countries and recruited 1817 women who were randomized to one of four daily treatment groups: folic acid (4 mg), folic acid (4 mg) with a multivitamin supplement, multivitamin supplementation without folic acid, or no supplementation at all. Participants were asked to use their supplements for one month prior to conception and throughout the first 12 weeks of pregnancy. The authors showed that women randomized to take folic acid supplementation had a 1.0% chance of having a child with an NTD (RR 0.28; 95% CI 0.12–0.71), but women in the unsupplemented arm did not show a decrease in the risk of NTD (RR 0.8; 95% CI 0.37–1.72).[12] Overall, supplementation with folic acid reduced the rate of recurrence of NTD by 72% (6/593 with folate supplements vs. 21/602 without).[12]

A second key trial evaluating folic acid-fortified multivitamin supplementation during pregnancy was a double-blind, randomized controlled trial in which 2104 women were randomized to take a 0.8 mg folic acid-containing multivitamin supplement, while 2052 women were randomized to take a multivitamin containing trace supplementation.[13] Supplementation began at least one month prior to pregnancy and continued to at least the time of the second missed menstrual period. Twenty-eight malformations were noted in the newborns in the folic acid-supplemented group, whereas 47 malformations were noted in the newborns in the trace supplement group.[13] No NTDs were observed in the babies in the folic acid-fortified group, whereas six NTDs were observed in the babies in the trace element group.[13]

The meta-analysis conducted by Motherisk found that multivitamin supplementation significantly reduced the risk of NTD, both in case-control studies (OR 0.67; 95% CI 0.58–0.77) and in cohort and randomized controlled studies (OR 0.52; 95% CI 0.39–0.69).[14]

The only available study investigating the relationship between serum and RBC folate concentrations and the risk of neural tube defects found an inverse relationship between maternal RBC folate and the risk of NTD.[15] Daly et al. showed in a case-control study that women receiving < 150 μg of folic acid daily had a risk of NTD of 6.6/1000 live births, and that women receiving > 400 μg daily had an NTD risk of 0.8/1000 live births. Supplementation at doses of 100 μg, and 400 μg daily resulted in a decrease in risk of NTD of 22%, 41%, and 47%, respectively.[16] Another study investigating dosing variations of folic acid corroborated this result, noting that daily folic acid doses of 100μg, 200 μg, and 400μg decreased the NTD risk by 18%, 35%, and 53%, respectively.[17]

Folic Acid and Other Malformations

In the Motherisk meta-analysis, we have shown that folic acid-containing prenatal vitamin supplements are also associated with a reduction in risk of oral clefts, heart defects, urinary tract anomalies, and limb anomalies in newborns.[14]

It could be argued that women who supplement with prenatal vitamins may have a lower risk of having children with malformations because they have better health and health-related behaviours than women not taking vitamins. However, in the case of neural tube defects[17] and oral cleft,[18] population-based studies have shown that the folate fortification program was associated with decreased risk, thus corroborating the associations shown in the meta-analysis.[14]

Early Pediatric Cancer

In a recent meta-analysis, we observed an apparent protective effect for early leukemia (OR 0.61; 95% CI 0.50–0.74), pediatric brain tumours (OR 0.73; 95% CI 0.60–0.88), and neuroblastoma (OR 0.53; 95% CI 0.42–0.68) associated with use of prenatal vitamin supplements containing folic acid.[19]

THE OPTIMAL DOSE OF FOLIC ACID SUPPLEMENTATION

For almost 20 years, the recommended daily dose of folate supplementation has been 0.4 mg. In fact, prenatal multivitamins invariably contain 0.8 to 1.1 mg of folic acid, and this has led to the assumption that daily supplementation with this dose is sufficient to prevent neural tube defects. However, in 2001, Wald systematically reviewed all reports of the correlation between ingested dose of folate and resultant serum concentrations.[19] Using the data of Daly et al.,[15] who correlated maternal serum folate levels with the risk of neural tube defects, Wald concluded that the currently recommended daily dose of folate will render only partial protection against neural tube defects. According to Wald's analysis, 5 mg per day of folate would be necessary to render 90% protection against NTD in the prenatal population.[19] Wald's analysis has been recently corroborated by our

ABBREVIATIONS

CI	confidence interval
NTD	neural tube defect
OR	odds ratio
RBC	red blood cell
RR	relative risk

Associations between folate status and risk of selected cancers, and folate status and risk of twinning

Breast cancer[23-39]	Meta-analysis: decreased cancer risk with high folate status
	Majority of case-control studies: reduction in risk (30-35%) at the highest dietary intake of folate status.
	May increase risk in post-menopausal women (non-significant statistically)
	Fortification with 5 mg folate is associated with a non-significant trend for increase in breast cancer mortality
Colorectal cancer[40-47]	Inverse relationship between folate status and risk of colorectal cancer in healthy people
	Potential increased risk of adenoma
Pancreatic cancer[48]	Decrease risk with higher folate status
Ovarian cancer[50,51]	Significant decrease in the serous subtype
	Prospective-prevention (non-significant trend)
Bladder cancer[52]	Significantly lower folate in cancer cases compared with controls
Carcinoma of head and neck[53]	Protective effect
Stomach cancer[54]	No effect
Esophageal, gastric,and pancreatic cancer[49]	Protective effect in case-control studies
Non-Hodgkin's lymphoma[55]	No correlation with folate status
Cervical cancer[56]	Folate fortification not associated in the degree or pattern of global DNA methylation in cells involved in cervical carcinogenesis
Twinning[59]	Systematic review: possible but non-significant evidence of periconceptional folate intake and twinning

finding that in 2005–2006, 40% of Ontario women did not achieve the protective red blood cell folate level of 900 nmol/L, despite flour fortification and despite the fact that more than 50% of pregnant women took prenatal multivitamin supplements.[20]

Before recommending prenatal supplementation with higher doses of folic acid, we need to consider the potential health risks of such a move.

It has been proposed that higher levels of folate intake may mask pernicious anemia arising from vitamin B12 deficiency. Similar concerns surrounded the original North American flour folate fortification program in 1998 but several recent studies have failed to show such a risk.[20] A recent US study suggested an association between high folate levels in older Americans and a risk of cognitive impairment.[21] However, cognitive impairment is not a component of pernicious anemia, and the study showed no increased risk for neuritis, which is a typical finding in patients with pernicious anemia. The risk for pernicious anemia will be different if the general population is consuming flour with higher levels of folate, rather than having pregnant women supplement their intake by 5 mg/day for a limited time. In fact, direct measurements of serum levels of vitamin B12, or higher dose supplementation of vitamin B12, may further allay these concerns.

If women do not comply with the recommendation to take the currently available folate-containing preparations, it is reasonable to question whether they would take the preparations containing 5 mg/day. In a recent controlled trial of prenatal vitamin supplements in women who discontinued or had not started taking prenatal vitamins, their compliance with two different brands of prenatal vitamins averaged 58% and ranged from 0 to 100% despite the participation of self-selected, motivated women.[22] Pharmacologically, administration of 5 mg of folate per day 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.[23–57] This trend towards reduction in cancer risk associated with folic acid use is shown in the Table. 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.[58] There is no question that an increased risk of cancer associated with folate use, even if it exists, is a result of long exposure to folate over years, and not to several months of dosing during pregnancy.

CONCLUSION

Unless the prescribing clinician can ensure that pregnant women will be perfectly compliant in using prenatal vitamin supplements containing 0.8 to 1.1 mg of folate, the prenatal

vitamin supplements should be combined with 5 mg of folate.

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