

Folate and neural tube defects: The role of supplements and food fortification

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Periconceptional folic acid significantly reduces the risk of neural tube defects. It is difficult to achieve optimal levels of folate by diet alone, even with fortification of flour, especially because flour consumption in Canada is slightly decreasing. Intermittent concerns have been raised concerning possible deleterious effects of folate supplementation, including the masking of symptoms of vitamin B₁₂ deficiency and an association with cancer, especially colorectal cancer. Both concerns have been disproved. The Canadian Paediatric Society endorses the following steps to enhance folate intake in women of child-bearing age: encouraging the consumption of folate-rich foods such as leafy vegetables, increasing the level of folate food fortification, taking a supplement containing folate and B₁₂, and providing free folate supplementation to disadvantaged women of child-bearing age. These recommendations are consistent with those of the Society of Obstetricians and Gynaecologists of Canada.

Key Words: Folate; Folic acid; Fortification; NTD; Supplementation

Folic acid (vitamin B₉) is a water-soluble B group vitamin. It is present in foods as folate and in supplements as folic acid, which has greater bioavailability. Folate plays an essential role in DNA synthesis and repair, and in cell growth and division. Folate also has a major role in DNA methylation and is therefore important for epigenomic regulation.

Folate is found in foods such as leafy vegetables, legumes and red meat. Offal, such as liver, also contains high levels of folate. However, up to 70% of folate can be lost during cooking due to thermal degradation or dissolution in the water used for cooking.(1,2)

Adequate folate intake is important for protecting against neural tube birth defects (NTDs). NTDs result from malformation or failed closure of the neural tube during central nervous system development in the third and fourth weeks of gestation.(3-11) NTDs include anencephaly, a failed closure of the neural tube at the cerebral cortex, and spina bifida, a defect of closure at the lumbosacral region or, less frequently, at higher regions of the spinal cord.(3,6,10-14) NTDs represent one of the most common categories of birth defects in North America. In 1996, the birth prevalence of neural tube defects in Canada (excluding Quebec) was 8 per 10,000 live births, with 219 affected infants.(6,15) In the period before folate fortification, the highest rates were reported in Eastern Canada, with rates decreasing progressively toward the West Coast: rates varied from 10 per 10,000 births in the East versus 5 per 10,000 births in the West.(6,15-18) There is a 2% to 5% risk of recurrence in women who have previously given birth to an affected child.(6,19)

Le folate et les anomalies du tube neural : le rôle des suppléments et des aliments enrichis

La consommation d'acide folique pendant la période périconceptionnelle réduit considérablement le risque d'anomalie du tube neural. Il est difficile d'atteindre un taux optimal de folate à partir du seul régime alimentaire, malgré l'enrichissement de la farine, surtout que la consommation de ce produit diminue légèrement au Canada. Les effets délétères possibles des suppléments de folate ont suscité sporadiquement des inquiétudes, y compris le camouflage des symptômes de carence en vitamine B₁₂ et une association avec le cancer, surtout colorectal. Ces deux inquiétudes ont été réfutées. La Société canadienne de pédiatrie appuie les mesures suivantes pour accroître la consommation de folate chez les femmes défavorisées en âge de procréer : encourager la consommation d'aliments riches en folate, comme les légumes-feuilles, accroître le taux d'enrichissement des aliments en folate, prendre un supplément contenant du folate et de la vitamine B₁₂ et distribuer gratuitement des suppléments de folate. Ces recommandations concordent avec celles de la Société des obstétriciens et gynécologues du Canada.

The etiology of NTDs is complex and multifactorial: genetics, chromosomal abnormalities and environmental factors have been implicated.(5,6,10,14,19-25) However, there is conclusive evidence that increased folic acid intake before conception is associated with a significant decrease in the birth prevalence of NTDs.(26) Optimal levels of total folate may also protect against congenital heart defects,(27) oral clefts,(28-29) and neurodevelopmental problems.(30) Current Health Canada recommendations are that women ingest at least 400 µg of folate per day to reduce the risk of bearing a child with an NTD. It is not commonly possible for most people to achieve this level of folate intake from natural foods and for this reason many countries, including Canada, the United States and the United Kingdom, have introduced initiatives to increase folate intake.(31-37) These initiatives include fortifying grain products with folic acid and promoting oral folic acid supplements.

FOLIC ACID FORTIFICATION OF FOODS

To address the dietary insufficiency in folate in North America, the fortification of flour and grain products (including ready-to-eat cereals and pasta) at a rate of 150 µg of folic acid/100 g was made mandatory in 1998. The objective of folic acid fortification is to reduce the birth prevalence of NTDs by increasing total maternal folate, best estimated by a determination of red blood cell (RBC) folate. Food fortification aimed to increase the daily folic acid intake by about 100 µg on average, and one American

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study demonstrated a rise in RBC folate concentrations from 527 nmol/L to 741 nmol/L in 38,000 women of child-bearing age following the introduction of folic acid fortification. However, even this policy still leaves only 23% to 33% (depending on ethnicity) of North American women of child-bearing age meeting the daily recommended intake.(38) As a result, RBC folate levels in some women remain below the optimal estimated protective level of 900 nmol/L.(39) Moreover, a recent large study in China with pharmacokinetic modelling showed that even higher levels of RBC folate (up to 1500 nmol/L) might be additionally helpful.(40)

Despite the fact that for many women daily folate intakes remain lower than the 400 µg Health Canada recommends, fortifying food with folic acid has been highly effective in reducing the birth prevalence of neural tube defects. Following folic acid fortification, the birth prevalence of spina bifida in Canada fell by over 50% and that of other NTDs by approximately one-third.(41) Moreover, the East-West gradient in the rates of NTDs flattened significantly following the introduction of folic acid fortification.(41) There may, however, be some under-ascertainment of cases because terminations at <20 weeks gestation/500 g are not uniformly recorded across the country. Similar 50% to 70% reductions in infants born with an NTD have been reported elsewhere following increased maternal folic acid intake.(12,23,35,39,42-44)

More recent studies of Canadian women of child-bearing age have revealed that approximately one-quarter of this population do not have protective levels of RBC folate,(45) despite some acknowledged discrepancies among assay techniques.(46) Supplement use was the most significant predictor of optimal levels and correlated with higher socio-economic status.(47)

ORAL FOLIC ACID SUPPLEMENTS

Despite overwhelming evidence that folic acid fortification is effective in reducing NTDs, a significant proportion of women remain folate-deficient in early pregnancy. Health Canada and the Public Health Agency of Canada recommend that women of child-bearing years take a daily supplement of 0.4 mg of folic acid to reduce the risk of NTDs. This recommendation is supported by detailed guidelines from the Society of Obstetricians and Gynaecologists of Canada.(13,17-18) They recommend that women in good health eat a diet of folate-rich foods, along with daily supplementation with a multivitamin which includes folic acid (0.4 mg to 1.0 mg) for at least two to three months before conception and throughout the pregnancy and postpartum periods (for a minimum of four to six weeks and as long as breastfeeding continues). Factors known to increase the risk of NTDs in subsequent pregnancies include birth of a previous child with a NTD, a family history of NTDs, maternal obesity and maternal Hispanic origin, and the use of some anti-convulsants.(48,49) Pregestational or gestational diabetes is of low predictive value,(48) perhaps because the risk may vary with the level of glycemic control.(50) Since the etiology appears to be multifactorial, each risk factor is of similarly low predictive value, with the highest risk being for women with a previous affected child (at 2% to 5% before fortification [24]). Therefore, for women with a family history of NTD or other health complications, the SOGC recommends increasing dietary intake of folate-rich foods and daily supplementation with multivitamins (including 5 mg of folic acid) at least three months before conception and continuing 10 to 12 weeks postconception.(18)

CHALLENGES WITH FOOD FORTIFICATION

While food fortification with folic acid has increased folic acid intake, it is estimated that only one-quarter of women of reproductive age take in a sufficient dietary total of folate to minimize the risk of having a child affected by an NTD.(32,51) When folic

acid fortification began in Canada in 1998, fortification was estimated to supply an extra 100 µg of folic acid daily to the average diet.(52) By 2008, however, the annual per capita consumption of flour in Canada had dropped by 2.3 kg from the previous year to 43.7 kg. This decline may have been due, in part, to a 35% increase in the cost of flour from 2007 to 2008, as well as to an increasingly popular trend toward adopting gluten-free diets. The total amount of folate being ingested as a result of food fortification is likely to have declined further since 2008.(53)

In the United States, populations at particular risk include women of Hispanic descent, especially those who are less acculturated or who eat less wheat flour and use more corn-based flour. Their levels of folic acid are lower and their rate of NTDs higher than in the non-Hispanic Caucasian population. There is a proposal to fortify corn masa flour to increase folate intake for these women,(54) who also have a relatively high incidence of a methylenetetrahydrofolate reductase (MTHFR) gene polymorphism (TT) that renders them at greater risk of low folate status.(55)

The current level of folic acid food fortification is below that required to enable most Canadians to attain the recommended daily intake (400 µg) from diet alone. It is reported that up to 40% of women of child-bearing age in Ontario do not achieve folic acid intakes sufficient to prevent NTDs in their children.(13,17-18) One more recent study found that in Canada overall, 25% of women of child-bearing age have suboptimal RBC folate levels.(45) Consequently, there is considerable debate around the level of folic acid fortification in foods and whether it should be increased to afford better fetal protection. In their 2007 guidelines, the SOGC proposed that folic acid fortification be increased to 300 µg/100 g of flour to better prevent neural tube defects. They also noted a positive impact on maternal health during pregnancy due to folic acid supplementation.(17-18)

CHALLENGES WITH SUPPLEMENTATION

Oral folic acid supplementation offers a more targeted approach for women of child-bearing age, and has been widely promoted. However, even though reasonable awareness of folate has been achieved through extensive marketing campaigns and clinical education, the adoption of folic acid supplementation is generally poor. Only one-quarter of North American women of child-bearing age take folic acid supplements. Also, there is a significant socio-economic gradient, with only 16% of women of low socio-economic status reported to have taken folic acid supplements during their pregnancy.(56) Those with annual earnings <\$25,000 USD cited the cost of folic acid supplements as an issue.(37) This statistic is especially important because low socio-economic status correlates with elevated risk for NTDs. It is women in these groups who are most in need of effective supplementation.(51,56-58) A recent small study from Ste-Justine Hospital in Quebec reiterated these findings, with only 4% of women who smoked and drank alcohol taking supplements in accordance with guidelines.(59) Alternative strategies include the use of oral contraceptives that contain a folic acid supplement, using tetrahydrofolate,(60) or recommending high-dose supplementation (5 mg daily). Counselling this higher dose assumes imperfect adherence, with only occasional supplements taken, but is safe and helps to achieve optimal RBC folate levels (www.motherisk.org/women/updatesDetail.jsp?content_id=891).

CONCERNS ABOUT FOLATE SUPPLEMENTATION: VITAMIN B₁₂ DEFICIENCY AND CANCER

There has been some hesitation to recommend increased levels of folic acid food fortification due to concerns around two issues: whether high levels of folate mask the symptoms of vitamin

B₁₂ deficiency and whether they are implicated in the etiology of colon and other cancers.

Folate, B₁₂ deficiency and pernicious anemia

Vitamin B₁₂ deficiency is generally diagnosed following presentation with pernicious anemia. Ingesting adequate levels of folate partially treats the anemia and may 'mask' the appearance of vitamin B₁₂ deficiency, possibly allowing neuropathy to progress and worsen.(7,35,39,62-64) However, more recent analysis of the effects of high folate intake has not confirmed the phenomenon of masking of symptoms of B₁₂ deficiency.(33,65-67) Epidemiological analysis has revealed that the number of cases of pernicious anemia has decreased rather than risen since the introduction of food folic acid fortification.(33,67,68) High intake of folate combined with low serum vitamin B₁₂ has been shown to actually exacerbate symptoms of B₁₂ deficiency rather than masking them,(65,66) whereas normal serum vitamin B₁₂ combined with high folate status demonstrated a protective effect against cognitive impairment.(67) These new findings suggest that increasing ingestion of folate at the level achieved with the current fortification standard poses no threat of masking vitamin B₁₂ deficiency. Current recommendations have shifted toward vitamin B₁₂ food fortification and finding more accurate ways to detect vitamin B₁₂ deficiency via blood assays.(33,61,63)

Folic acid and cancer

Folate antagonists such as methotrexate are part of the chemotherapeutic arsenal used in the treatment of cancer. It is therefore reasonable that there has been some concern as to whether increasing the levels of folate in the population acts to either initiate or promote cancer, perhaps by providing a permissive environment for the growth of pre-existing cancers.

Several reviews have found either no increase or a slight decrease of cancer risk in people with the highest folate status, with individual studies variously controlling for possible confounding variables (eg, age, sex, caloric, fibre and alcohol intake, body mass index and family history). The cancers reviewed include colorectal, breast, prostate, pancreatic and lung cancer:

Breast cancer is by far the most common malignancy in women and in Canada, it is responsible for 27% of all incident cases and 15% of cancer deaths in women. One review and meta-analysis of breast cancer studies showed no association between breast cancer and the use of multivitamins, including folic acid.(68,69)

Prostate cancer is the most common malignant disease in men, and accounts for 28% of all incident cases and 11% of cancer deaths in men. A recent study presented findings of the largest case-control study of prostate-specific antigen test detected prostate cancer to date, including a review and meta-analysis of prostate cancer risk and folate. Results were inconclusive, although study authors were unable to rule out some association between high folate status and increased prostate cancer risk.(70)

Pancreatic cancer is the fourth-leading cause of cancer death in both men and women, accounting for around 5% of all cancer deaths and a little over 2% of incident cases. One review suggests that for women, higher levels of folate protect against pancreatic cancer, while for men there is no effect.(71)

Lung cancer is by far the biggest single cause of cancer death in men and women, accounting for 27% of all cancer deaths. The European Prospective Investigation into Cancer and Nutrition (EPIC), a large cohort study with participants in 10 countries, published their main finding in this area: a substantive reduction in the risk of lung cancer in people with the highest folate status.(72)

Colorectal cancer is the third most common cancer in men and women, accounting for 14% and 12% of all incident cases,

respectively, and a similar proportion of cancer deaths. One study proposed the hypothesis that increased folate intake heightened the risk of colon cancer in adults, acting as a cancer promoter.(36,73) A possible 'dual modulatory' effect has been noted in model systems, in which folate deficiency has an inhibitory effect while supplementation may promote cancer growth in already established colorectal neoplasms.(74) However, folate-deficient colorectal cells were protected from neoplastic changes by the addition of modest concentrations of folate in rodent models.(74) The epidemiological evidence for a relationship between colorectal cancer and folate has been extensively reviewed with the conclusion that high folate status reduces the risk of colorectal cancer.(73,75) A linear inverse relationship between folate status and colorectal cancer risk has been clearly demonstrated. The greatest difference found was between those in the highest and lowest quintiles. Individuals in the highest quintile were the most likely to take multivitamin supplements containing folate in an especially bioavailable form (as pteroyl-monoglutamic acid), as well as other potentially important micronutrients.(73)

OTHER CONCERNS

Other concerns that have been raised but not supported by the evidence include an increased risk of bronchiolitis in the infants of supplemented mothers,(76) anorectal malformations,(77) preeclampsia,(78) acute lymphoblastic leukemia(79) and brain tumours.(80) Unmetabolized folic acid in supplemented patients has also been suggested as a possible cause of disease, but this concern has not withstood scrutiny.(81)

SUMMARY

The impact of folic acid fortification and supplementation on reducing NTDs is well established and has led to mandatory food fortification in more than 50 countries, including Canada.

Despite flour fortification at current levels, the recommended daily intake of 400 µg is difficult to achieve for a variety of reasons, including relatively poor availability of folate in natural foods and its easy destruction during cooking. A lower general consumption of flour and a trending socio-economic gradient in folate intake from all sources leave many pregnancies underprotected against NTDs.

Currently, at least 25% of women of child-bearing age do not have folate intake sufficient to optimally protect their offspring from NTDs. Inequality remains, with women of lower socio-economic status being less well protected by folate. As a consequence, they bear the greatest burden of this serious congenital anomaly.

Concerns that folate supplementation increases the risk of cancer or masks vitamin B₁₂ deficiency appear to be unfounded.

RECOMMENDATIONS

It is essential that women of child-bearing age maximize protection of their offspring from the risks of neural tube defects (NTDs) by ensuring adequate folate intake. Folate is available from three sources: natural diet, food fortification and oral supplementation. Folate intake from all sources should be promoted by policy makers and health professionals:

Natural diet: The significance of eating folate-rich foods such as leafy vegetables should continue to be a fundamental message delivered to all women of child-bearing age, especially those known to be contemplating pregnancy. This strategy is consistent with "Canada's Food Guide" from Health Canada and with recommendations from the Society of Obstetricians and Gynaecologists of Canada (SOGC).

Food fortification: Flour and cereal products in Canada are supplemented at the level of 150 µg/100 g. This level was based on dietary intake of these products in the 1990s. In light of lower flour

consumption, strong evidence that maternal dietary folate intake remains inadequate and a growing body of evidence to suggest a cancer-protective (rather than carcinogenic) effect of higher folate intake, the Canadian Paediatric Society strongly recommends increasing the level of folic acid food fortification.

Oral supplementation: Health Canada guidelines advise women of child-bearing age to take a daily multivitamin tablet containing 0.4 mg of folate as well as vitamin B₁₂. The SOGC advocates a much higher intake for women at risk because of their current health status or a family history of NTD. The Canadian Paediatric Society supports this recommendation and, in addition,

recommends supplementation with folate for all women during the child-bearing years. The Canadian Paediatric Society also strongly recommends providing free folate supplementation for women of child-bearing age, particularly those in less advantaged circumstances, for whom the risk of not achieving adequate prophylaxis is highest.

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