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Folic Acid Supplementation for Pregnant Women and Those Planning Pregnancy: 2015 Update

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Abstract

During the last decade critical new information has been published pertaining to folic acid supplementation in the prevention of neural tube defects (NTDs) and other folic acid–sensitive congenital malformations. These new data have important implications for women, their families, and health care professionals. We performed a review looking for the optimal dosage of folic acid that should be given to women of reproductive age who are planning or not avoiding conception to propose updated guidelines and thus help health care providers and patients. In addition to fortification of dietary staples with folic acid, women of reproductive age should supplement before conception with 0.4-1.0 mg of folic acid daily as part of their multivitamins. In the United States all enriched rice is also fortified with folic acid at 0.7 mg per pound of raw rice. However, this is not the case in many countries, and it has been estimated that only 1% of industrially milled rice is fortified with folic acid. In countries where rice is the main staple (eg, China), this does not allow effective folate fortification. Whereas the incidence of NTDs is around 1/1000 in the United States, it is 3- to 5-fold higher in Northern China and 3-fold higher in India. A recent population-based US study estimated that the reduction in NTD rates by folic acid is more modest than previously predicted. The potential of NTD prevention by folic acid is underutilized due to low adherence with folic acid supplementation, and calls for revising the policy of supplementation have been raised. We identified groups of women of reproductive age who may benefit from higher daily doses of folic acid, and this should be considered in current practice. These include women who have had previous pregnancies with NTDs, those who did not plan their pregnancy and hence did not supplement, and women with low intake or impaired adherence to daily folic acid supplementation. In addition, women with known genetic variations in the folate metabolic cycle, those exposed to medications with antifolate effects, smokers, diabetics, and the obese may benefit from higher doses of folic acid daily during the first trimester.

Keywords

folic acid, folate, neural tube defects, prevention, genetics of neural tube defects, spina bifida

After decades of speculation regarding the role of folic acid supplementation in the prevention of neural tube defects (NTDs), two randomized controlled studies published in the early 1990s demonstrated that folic acid supplementation can indeed prevent the occurrence and recurrence of these malformations. In studying families with previous NTDs, Wald et al have shown the effectiveness of supplementing with 4 mg/day of folic acid.[1] In studying families with no history of NTDs, Czeizel et al subsequently demonstrated the effectiveness of supplementation with 0.8 mg/day as part of prenatal vitamins starting before conception to reduce the occurrence of NTDs.[2] As a result of these studies, the FDA, Health Canada, and similar authorities worldwide implemented policies to fortify flour with folic acid starting in 1997–1998.[3] The results were dramatic, with up to a 50% decrease in the rates of NTDs. However, a recent population-based US study estimated that the reduction in NTD rates by folic acid is more modest than previously predicted. The potential of NTD prevention by folic acid is underutilized due to low adherence with folic

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acid supplementation, and calls for revising the policy of supplementation have been raised.[4] To date, over 50 countries including China have moved to fortify flour and other food staples with folic acid, which has resulted in a dramatic decrease in the occurrence and recurrence of NTDs. In the United States, all enriched rice is also fortified with folic acid at 0.7 mg per pound of raw rice. However, this is not the case in many countries, and it has been estimated that only 1% of industrially milled rice is fortified with folic acid. In countries where rice is the main staple (eg, China), this does not allow effective folate fortification. Whereas the incidence of NTD is around 1/1000 in the United States, it is 3- to 5-fold higher in Northern China and 3-fold higher in India.

During the last decade important new information has been published pertaining to the association of folic acid supplementation and the risk for occurrence and recurrence of NTDs as well as other folic acid–sensitive congenital malformations. These new data have important implications for women, their families, and health care professionals. The objective of this update is to incorporate these new data into practice in women who are planning to conceive or who have already conceived.

Methods

MEDLINE, EMBASE, Web of Science, and the Cochrane Library were searched from inception to January 15, 2015 to identify studies in any language that addressed the effects of folic acid on reducing the risk of congenital malformations and other pregnancy outcomes. The focus of this review was studies that answered the question: What is the optimal dose for the prevention of NTDs and other adverse fetal outcomes?

The data were reviewed and analyzed along 2 domains:

> Pharmacokinetic: the concentrations of folic acid needed to prevent NTDs and other malformations, and the daily dose needed to achieve these concentrations.
> Pharmacodynamic: conditions and factors that may modify the dose/level-response of folic acid. The pharmacodynamic domain has been largely ignored in previous guidelines, with the assumption that the protective concentrations can be generalized and apply to all women.

Pharmacokinetic Considerations

In 1995 Daly et al documented that maternal red blood cell (RBC) concentrations of folic acid of 906 nM confer optimal protection against NTD, with rates increasing in a dose-response manner.[5] Daly's data implied that RBC folate concentrations above 906 nM could not further decrease the incidence of NTD. Hence, over the ensuing 2 decades this RBC concentration reference has become the target of numerous public health interventions to prevent this serious group of birth defects. Daly's study was based on a sample of 84 Irish women who carried babies with NTD and 266 controls whose RBC folate was measured at 15 weeks of gestation.

However, although serum folate concentration changes are based on recent intake, RBC folate reflects the long-term body status of folate and hence confers better predictive value of protective folate concentrations.

In 2014 Crider et al published the results of 2 cohorts collected in China: a prospective intervention study to prevent NTD that included 247,831 women and a second cohort of 1194 women in a randomized population-based study of preventing NTDs with daily folic acid supplementation of 0.1 mg/day, 0.4 mg/day, 4 mg/day, or 4 mg/week.[6] Using Bayesian modeling, they confirmed the protective effect of folic acid supplementation in the prevention of the occurrence of NTDs. However, based on a significantly larger number of cases than Daly et al,[5] Crider et al concluded that the rates of NTDs can be further reduced in some cases when RBC folate concentrations are increased up to 1500 nM, which represents up to a 66% higher concentration than that used by Daly et al and would allow room for higher doses of folic acid supplementation associated with a greater degree of protection.

In 2001 Wald et al suggested, based on analysis of published studies, that supplementation of folic acid at 0.4 mg/day (as suggested by most publications) or 0.8–0.9 mg/day (the content of most prenatal vitamins) would not produce a RBC concentration of 906 nM in many of the women.[7] Indeed, in 2005 in Ontario, 40% of women were not achieving, preconceptionally, RBC concentrations of 900 nM despite food fortification.[8]

This is not surprising because there is intersubject variability in many factors associated with folic acid metabolism and response, such that higher daily doses of this vitamin may be needed to maximize its protective effect on the fetus.

A potentially important pharmacokinetic variable is the time needed to achieve a steady-state concentration of folic acid in a woman planning pregnancy. Several new studies have addressed this question, showing that in a person who was not sufficiently supplemented with folic acid by diet or through a multivitamin, it may take up to a year to achieve a stable steady-state concentration with 1 mg/day folic acid supplementation.[9] Typically, in North America, people consume folic acid from food fortification at a mean daily amount of 138 μg.[10]

Poor compliance with folic acid supplementation can take different forms:

> An estimated 50% of women do not plan their pregnancy and hence may not start folic acid

supplementation before conception. Given that the closure of the neural tube is completed by 28 days postconception, there is a narrow window of opportunity from the time the woman finds out she has conceived and the end of the prevention window. It makes pharmacological sense to provide such women with a higher dose of folic acid with the aim of achieving high serum concentrations of folic acid for the developing neural tube. Recent studies have shown that a daily supplement of 5 mg folic acid provides attendant serum concentrations with an area under the concentration-time curve (AUC) 5-fold higher than with the typical 1-mg daily dose.[11] In contrast, RBC concentrations increased by only 2-fold. For these women, the window of opportunity for the prevention of NTD may be brief, and a high dose of folic acid may be more effective in bringing the concentrations into the desired range.

Many women do not consume sufficient amounts of folic acid through their diet. Typically, they do not eat sufficient servings of vegetables rich with folate such as beans, lentils, spinach, and other leafy vegetables from organic sources without any processing such as canning or heavy cooking.

A large number of women try to reduce their consumption of carbohydrates and hence may avoid bread and other flour-based products fortified with folic acid. Typical Canadian and American fortification provides on average 140 μg per day of folic acid. Of future importance, the form of l-5-methyl-tetrahydrofolate (THF) is also available commercially as a crystalline form of the calcium salt (Metafolin).

Intake of l-5-methyl-THF may have several potential advantages over folic acid. First, the potential for masking the hematological symptoms of vitamin B_{12} deficiency may be reduced with l-5-methyl-THF. Second, l-5-methyl-THF may be associated with a reduced interaction with drugs that inhibit dihydrofolate reductase.

There are increasing numbers of women avoiding gluten for conditions such as celiac disease; avoiding gluten-containing flour products means that these women do not benefit from folic acid fortification of flour.[12]

Even women who take prenatal vitamins exhibit varying degrees of adherence to them, and often women object to the perception of "medicalization" of their pregnancies. Other women may not take recommended prenatal vitamins because of fear of nausea and vomiting.[13] Furthermore, natural food folates are unstable compounds, and losses in vitamin activity can be expected during food processing. Thus, up to 70% of folates can be destroyed by milling and baking.[14]

Oral Contraceptives

For decades it was suspected that the oral contraceptives decrease systemic levels of folic acid. This has been recently confirmed through meta-analysis of 27 studies, indicating that women on oral contraceptives may need higher doses of folic acid to achieve the needed protective concentrations.[15]

Malabsorption Syndromes

With women postponing the start of their families into their 30s or 40s, up to 5% of women of reproductive age are estimated to have conditions associated with malabsorption such as Crohn disease, such that effective absorption of folic acid in the ileum cannot be assumed.[16]

Polymorphisms in the Genes Involved in Folic Acid Metabolism and Receptors Associated With Neural Tube Defects

As this field is rapidly expanding, we will exemplify several polymorphisms that can affect folate concentrations and effects. The methylenetetrahydrofolate reductase (MTHFR) genotype is associated with modification of the risk for neural tube defects. MTHFR TT was associated with lower folate concentrations, and the trend of TT < CC was maintained at even the high doses.[17]

Folate is an essential B vitamin that is involved as a cofactor in critical metabolic pathways that involve both DNA synthesis and methylation. Several of the single nucleotide polymorphisms (SNP) of the enzymes in these critical pathways have been investigated for their involvement in the failure of neural tube closures in human.

Synthetic folic acid is in the monglutamate form and does not require this enzyme for absorption. Autoantibodies directed against the folate receptor, blocking the binding of folic acid and inhibiting folate uptake, have been identified in a small study of women whose pregnancy was complicated by NTDs.[18]

Another SNP that encodes for reduced folate receptor has been identified, A80G, which results in an impaired ability to transport folates into the cytoplasm.[19] This SNP has been associated with neural tube defects, particularly when there was a lack of maternal prenatal folic acid supplementation.[19–22]

One SNP in the methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) gene, G1958A, has been identified to confer an increase risk for having a child with a NTD. MTHFD provides 10-formyl-THF, which is essential for purine synthesis. Inadequate availability of folate for purines may result in DNA breaks and chromosome damage.[23] A base pair deletion in the dihydrofolate reductase (DHFR) gene has been demonstrated to increase the risk of having a child with spina bifida.[24]

The polymorphism MTHFR C667T, which results in a thermolabile form of the enzyme, has been extensively studied for its association with NTDs. A 2000 meta-analysis

by Botto and Yang found that mothers with this polymorphism were at a 2-fold increase of having a child with NTD (odds ratio 2.0 [95%CI 1.5–2.8]), while infants with this polymorphism had an 80% increase in NTD risk (odds ratio 1.8 [95%CI 1.4–2.2]).[25] A second SNP in this gene, A1298C, has also been associated, in one study, with an increased risk for NTDs.[26] This polymorphism also results in reduced activity of the enzyme; however, not to the same extent as the C667T polymorphism.

A base pair repeat sequence has been identified in the gene that encodes for the enzyme thymidylate synthase, which, when expressed as a double repeat sequence, is associated with an increased risk for NTD.[27] Polymorphisms are associated with risk of not achieving protective systemic concentrations of folic acid. Because polymorphisms in these genes are not routinely tested in pregnant women, a reasonable approach is to increase dietary folic acid prior to conception and during organogenesis.

Pharmacodynamic Considerations

There are an increasing number of recently indentified factors that lead to the need for higher doses of folic acid to overcome pharmacodynamic factor(s) that inhibit the protective effect of folic acid. Some of these pharmacodynamic factors have been documented in humans, whereas others have only been demonstrated in experimental models.

A Previous Pregnancy With NTD

Although the risk of having a child with NTD in the general population in North America is presently less than 1:1000, the recurrence risk following a pregnancy/birth of a child with NTD is 40-fold higher at approximately 4%.[1] In the breakthrough randomized controlled MRC trial by Wald and colleagues, a daily dose of 4 mg/day of folic acid decreased this risk by 72% when compared to women who did not receive folic acid supplementation. Hence, it is critical to provide supplementation with folic acid 4-5 mg/day 2-3 months prior to conception and during the first trimester of pregnancy to women under these circumstances. In general the risk depends on the general population risk and is about 14 times for first-degree relatives. Thus, if the incidence in the general population is 1/500, the recurrent risk is 7%.

Exposure to Drugs With Antifolate Activity

Women exposed to medications with anti–folic acid action including antiepileptic drugs (carbamazepine, valproate, barbiturates), sulfonamides, and methotrexate[28] have shown an increased risk of NTD.

There is experimental evidence to show that higher doses of folic acid can prevent NTDs associated with in utero exposure to valproic acid.[29,30] Moreover, for all antifolate antiepileptics a dose-response relationship has recently been documented between drug dose and adverse outcome, indirectly suggesting that higher doses of folic acid may be more effective in preventing NTDs.[31] Although ethically it is not possible to randomize women to receive/not to receive folic acid at different doses for the purpose of showing prevention of NTD by higher vs regular doses of folic acid, it is logical to offer them higher doses of folic acid 2–3 months prior to conception and through the first trimester of pregnancy, as they may more effectively prevent NTDs.

Obesity

A large number of studies have confirmed an increased risk of NTDs among obese women.[32] With rates of obesity increasing dramatically among North American women of reproductive age, studies have shown that the increased risk for NTDs among obese women is sustained even with appropriate folate intake. Although there are no intervention studies to prove that higher folic acid doses would be effective in modifying such increased risk, it is conceivable to offer these women the benefit of such potential. Here again, although the mechanism(s) leading to an increased risk of NTDs have not been elucidated, it is reasonable to try to address them by providing an increased folate dose for a brief time before and during pregnancy to possibly obviate a yet unidentified pharmacodynamic factor increasing their risk.

Smoking

Up to 23% of American women enter pregnancy as smokers. Repeated studies have shown increased risk of NTD among pregnant women subjected to active and passive smoking.[33] Here too, although the mechanisms leading to increased risk of NTDs have not been elucidated, it is reasonable to try and prevent them by avoiding active and passive smoking as well as increasing folate supplementation for a brief period of time.

Diabetes

Several studies have documented a 10-fold increase in the incidence of NTD among women with poorly controlled diabetes during the first trimester of pregnancy.[34] Since periconceptional control of diabetes mellitus in pregnant women is difficult, the use of high-dose folic acid supplementaion may decrease the risk for having a baby with NTD.

Are There Maternal or Fetal Risks Associated With Folic Acid Supplementing at 4–5 mg/day?

To date, no study has documented increased fetal risks associated with maternal exposure to 4–5 mg/day of folic acid. A recent observational study from Spain suggested there may be increased neurocognitive risks when the dose of folic acid exceeded 5 mg/day. However, this finding was based on very small numbers of patients, and the risk emerged only above 5 mg/day.[35]

Reports suggested increased risk of colon cancer associated with prolonged use of high-dose folic acid. However, these claims have not been substantiated by systematic reviews of both randomized and observational studies[36–38] and are not relevant for the shorter periods of needed supplementation in the context of pregnancy.

Moreover, new studies have documented that although an increase of folic acid dose from 1.1 mg to 5 mg results in a 5-fold increase in AUC of a single dose, steady-state concentrations are increased by only 2-fold, indicating that, similar to iron and other essential micronutrients, the body may take "as much as it needs" and limits excessive absorption.[39,40]

Recent studies suggest epigenetic changes with high-dose folic acid in animals,[41] but the relevance of these findings to short use in human pregnancy has not been established.

There are also a couple of studies that suggest that high-dose folic acid may be associated with a slight increase in the risk for infant asthma.[42,43]

Synthesis of the Data

The general recommendation of folic acid supplementation at 0.4 mg/day of folic acid may be appropriate for healthy and normal-weight women without the risk factors detailed above, who sustain this intake for at least 6 months prior to conception. Prenatal vitamins typically containing 0.8–1 mg of folic acid will confer appropriate protection if used for at least 3–6 months.

The groups of women who may benefit from taking 4–5 mg/day of folic acid, either singly or as part of a prenatal vitamin regimen when planning pregnancy are listed in Table 1.

This higher dose should not continue beyond the first trimester of pregnancy. When one combines the prevalence of these risk groups, it is evident that a significant proportion of pregnant women belong to at least 1 of these categories, with obesity alone affecting an estimated 20% of North American women of reproductive age, smoking 15%, and malabsorption 5%. It has been estimated that the overall adherence rate with folic acid tablets is only 50%. It is important that women understand that they should not attempt to get their additional folic acid by taking more than 1 daily dose of a standard prenatal vitamin, as this approach will result in excessive doses of other components of the multivitamin preparation. Women can take a single 5-mg folic-acid-only tablet or combine it with other prenatal vitamins.

Table 1. Who Is at Increased NTD Risk?

1. Previous pregnancy with NTD
2. Close family member with NTD
3. Obesity
4. Use of drugs with antifolate effects.
5. Genetic mutations in the folic acid metabolic pathway or folate receptors
6. Poorly controlled type 1 or type 2 diabetes mellitus
7. Poor compliance with folic acid supplementation
8. Smoking, passive or active
9. Use of oral contraceptives
10. Celiac and Crohn diseases

Many of the proposed guidelines are reflected in the 2015 guidelines by the International Federation of Obstetrics and Gynecology (FIGO) published in January 2015,[44] although FIGO acknowledges that there is a paucity of data on the effects of high-dose folic acid.

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