Identifying women who might benefit from higher doses of folic acid in pregnancy

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Abstract

Question One of my epileptic patients who takes carbamazepine is planning to become pregnant. She told me that Motherisk advised her to take 5 mg of folic acid daily until the end of the first trimester. Are there other women who need more than the regular dose of folic acid included in prenatal vitamins?

Answer Women who are at high risk of having babies with neural tube defects and who would benefit from higher doses of folic acid include those with certain folate-enzyme genotypes, previous pregnancies with neural tube defects, diabetes, malabsorption disorders, or obesity, or those who take antifolate medications or smoke. Such women should take 5 mg/d of folic acid for the 2 months before conception and during the first trimester.

Identifier les femmes susceptibles de bénéficier de doses plus élevées d'acide folique durant la grossesse

Résumé

Question Une de mes patientes prend de la carbamazépine pour l'épilepsie et planifie une grossesse. Elle m'a dit que Motherisk lui avait conseillé de prendre 5 mg d'acide folique jusqu'à la fin du premier trimestre. Y a-t-il des femmes qui ont besoin d'une dose plus élevée d'acide folique que celle contenue habituellement dans les vitamines prénatales?

Réponse Parmi les femmes à risque élevé d'avoir un bébé ayant une anomalie du tube neural (ATN) et qui bénéficieraient de doses plus élevées d'acide folique, on peut mentionner celles qui ont certains génotypes associés aux enzymes de synthèse du folate, qui ont eu une grossesse antérieure ayant pour issue une ATN, qui sont atteintes de diabète, qui ont des problèmes de malabsorption, qui sont obèses, qui prennent des médicaments antifoliques ou qui fument. Ces femmes devraient prendre 5 mg/j d'acide folique 2 mois avant la conception et durant le premier trimestre de grossesse.

At the beginning of the 1990s, 2 randomized controlled studies showed that folic acid supplementation could prevent most neural tube defects (NTDs).[1,2] In studying women with previous NTD-affected pregnancies, Wald et al found that 4 mg/d of folic acid was an effective dosage.[1] In studying families with no previous cases of NTDs, Czeizel and colleagues showed the effectiveness of 0.8 mg/d of folic acid supplementation starting before conception.[2] As a result of these studies, the US Food and Drug Administration, Health Canada, and similar authorities worldwide agreed to fortify flour with folic acid starting in 1997 to 1998. The results were dramatic, with an up to 50% decrease in rates of NTDs.[3]

Yet, as stated by Wald et al in 2001, supplementation of folic acid at 0.4 mg/d (as suggested by most authorities) or 0.8 to 0.9 mg/d (the amount contained in most prenatal vitamins) did not produce protective levels in many women.[4] Indeed, in 2008 Motherisk found that, in Ontario, 40% of women did not achieve the protective red blood cell folate level of 900 nmol/L before conception.[5]

This is not surprising, as intersubject variability in many factors associated with folic acid metabolism and response has been clarified during the past decade, suggesting that higher daily doses of this vitamin might be needed to maximize its protective effect on the fetus.

The aim of this article is to highlight the clinical factors and conditions for which there is published evidence for increased risk of NTDs or other folic acid–sensitive congenital malformations. These pregnancies might benefit from higher doses of folic acid before conception and during the first trimester of pregnancy (**Box 1**).

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Polymorphisms associated with NTDs

Folate is an essential B vitamin that acts as a cofactor in critical metabolic pathways, which involve both DNA synthesis and methylation. Several single nucleotide polymorphisms (SNPs) of the enzymes in these critical pathways have been investigated for involvement in the failure of neural tube closure in humans.

Naturally occurring folates are polyglutamated. These must be converted to their monoglutamate form before they can be absorbed from the gastrointestinal tract into circulation. The enzyme folylpoly-γ-glutamate carboxypeptidase II is responsible for the hydrolysis of the polyglutamyl chain of naturally occurring folates. This enzyme is located on the apical aspect of the intestinal brush border.[6,7] Once in monoglutamate form, folate is absorbed

Box 1. Women who might benefit from higher doses of folic acid in pregnancy

The following pregnant patients are at increased risk of NTDs and might benefit from higher doses of folic acid:
Patients with ...
- specific genotypes associated with higher risk of NTDs
- previous pregnancies with NTDs or family history of NTDs
- malabsorption disorders (eg, inflammatory bowel disease)
- obesity with BMI > 35 kg/m^2
- diabetes
- compliance and lifestyle issues

Patients who ...
- take antiepileptic drugs
- take folate antagonists (eg, methotrexate, sulfonamides)
- smoke
- belong to high-risk ethnic groups (eg, Sikh, Celtic, Northern Chinese)

BMI—body mass index, NTD—neural tube defect.

by the reduced folate carrier (RFC) and enters the blood stream as 5-methyltetrahydrofolate, a monoglutamate. 5-Methyltetrahydrofolate is carried into the cytoplasm of cells through folate receptors (FRs) α, β, and γ and the RFC.[7] Folate receptors β and γ and the RFC have lower affinity for 5-methyltetrahydrofolate than the FR α.[7,8] Expression of FR α is limited predominantly to the kidneys, choroid plexus, and placenta, while the RFC is ubiquitously expressed.[9,10]

A polymorphism has been demonstrated in the glutamate carboxypeptidase II gene C1561T, which codes for the enzyme folylpoly-γ-glutamate carboxypeptidase II.[11] The SNP results in reduced activity of the enzyme and reduced plasma folate levels.[11] Synthetic folic acid is in the monoglutamate form and does not require this enzyme to be absorbed.[11] Autoantibodies directed against the FR, blocking the binding of folic acid and inhibiting folate uptake, were identified in a small study of women whose pregnancies had been complicated by NTDs.[11]

Another SNP that encodes for the RFC has been identified, A80G, which results in an impaired ability to transport folates into the cytoplasm.[12] This SNP has been associated with NTDs, particularly when there is a lack of maternal prenatal folic acid supplementation.[12-15]

Once inside the cell, 5-methyltetrahydrofolate acts as a methyl donor in several ways. The remethylation of homocysteine to methionine is enzymatically driven by methionine synthase, which results in conversion of 5-methyltetrahydrofolate to tetrahydrofolate and methionine. Tetrahydrofolate is acted upon by serine hydroxymethyltransferase

and converted to 5,10-methylenetetrahydrofolate. 5,10-Methylenetetrahydrofolate can then be used in various pathways. It can be converted by methylenetetrahydrofolate dehydrogenase to 10-formyltetrahydrofolate for purine synthesis; be irreversibly converted to 5-methyltetrahydrofolate by methylenetetrahydrofolate reductase; or operate as a methyl donor in the conversion of deoxyuridylate by thymidylate synthase, resulting in thymidine monophosphate and dihydrofolate. Dihydrofolate is converted to tetrahydrofolate via the enzyme dihydrofolate reductase.

An SNP in the methylenetetrahydrofolate dehydrogenase gene, G1958A, was found to confer an increased risk of having an NTD-affected child.[16] Methylenetetrahydrofolate dehydrogenase provides 10-formyltetrahydrofolate, which is essential for purine synthesis.[17] Inadequate availability of folate for purines might result in DNA breaks and chromosome damage.[17]

A base-pair deletion in the dihydrofolate reductase gene has been shown to increase the risk of having a child with spina bifida.[18]

A polymorphism in methylenetetrahydrofolate reductase C667T, which results in a thermolabile form of the enzyme, has been extensively studied in association with NTDs. In a 2000 meta-analysis, Botto and Yang found that mothers with this polymorphism were at a 2-fold increased risk of having children with NTDs (odds ratio 2.0, 95% CI 1.5 to 2.8), while infants with this polymorphism had an 80% increased risk of NTDs (odds ratio 1.8, 95% CI 1.4 to 2.2).[19] A second SNP in this gene, A1298C, has also been associated with NTDs.[20] This polymorphism also results in reduced activity of the enzyme, but not to the same extent as the C667T polymorphism does.

A base-pair repeat sequence was identified in the gene that encodes for the enzyme thymidylate synthase, which, when expressed as a double repeat sequence, was associated with an increased risk of NTDs in infants.[21]

Because these SNPs are associated with a risk of not achieving protective systemic levels of folic acid, clinicians should offer women known to have such polymorphisms 5 mg/d of folic acid before conception and until the end of the first trimester (ie, until after closure of the neural tube).

Previous pregnancy with NTD

While the risk of NTDs in the general population in North America is currently less than 1 per 1000 pregnancies, the risk in women with previous pregnancies with NTDs is 40-fold higher, at around 4%.[1] In the breakthrough randomized controlled trial by Wald et al, 4-mg/d of folic acid decreased this risk by 75% compared with women who did not receive folic acid supplementation.[1] Therefore, it is critical to provide the available 5-mg/d folic acid supplement to women with previous NTD-affected pregnancies.

Exposure to drugs with antifolate activity

Women planning pregnancy might be exposed to medications with known antifolate activities affecting different parts of the folic acid metabolic cascade. A relatively large number of epidemiologic studies have shown an increased risk of NTDs among babies exposed in early gestation to antiepileptic drugs (carbamazepine, valproate, barbiturates), sulfonamides, or methotrexate.[22]

Hence, whenever women use these medications, or have used them near conception, they should take 5 mg/d of folic acid until the end of the first trimester of pregnancy.

Maternal conditions

As more women postpone starting their families into their 30s or 40s, up to 5% of women of reproductive age are estimated to suffer from malabsorption syndrome because of conditions such as Crohn disease. These women often absorb folate suboptimally. Obese women also have a higher risk of NTDs in their offspring, as do women with type 1 or 2 diabetes mellitus, even after correction for insufficient folate supplementation.[23]

Suboptimal adherence

In a recent study, we showed that even women volunteering to take folic acid had low overall adherence of 53% (ranging from 0% to 100%).[24] If you suspect or have proof of low compliance, it is logical to prescribe 5 mg/d of folic acid, as it will ensure that the woman meets the folic acid requirement even if she takes the supplement sporadically.

Conclusion

Pregnant women with many of the conditions discussed above will not necessarily have levels of folic acid below the protective range. However, it appears that their relative resistance to folic acid necessitates higher doses, up to 5 mg/d for a short period, encompassing the prepregnancy months and the first 3 months of pregnancy.

Concerns that excess folic acid might increase later risk of colon cancer have been addressed by numerous studies and meta-analyses, which have failed to show such an association.[25] More important, pregnant women would only be exposed to 5 mg/d of folic acid for several months and not for the many years that these studies focused on.

It is important to offer selected high-risk women folic acid doses above the amounts contained in typical prenatal vitamins. While most pregnant women would benefit from daily folic acid doses of 0.4 mg through diet, or folic acid doses of 0.8 to 0.9 mg/d as found in most prenatal vitamins, selected groups of women at high risk might benefit from daily folic acid doses of 5 mg starting from 2 months before conception up to the end of the first trimester. These women include those with previous children with NTDs, specific genotypes related to folic acid metabolism, diabetes mellitus, or malabsorption syndrome, or those women who are exposed to antifolate drugs, are obese, or smoke, as well as women with proven or suspected low adherence with folic acid supplementation.

Competing interests

Dr Koren serves as a paid consultant for Bayer Inc and Duchesnay Inc, producers of prenatal vitamins and folic acid.

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