THE USE OF FOLIC ACID FOR THE PREVENTION OF NEURAL TUBE DEFECTS AND OTHER CONGENITAL ANOMALIES

Abstract
Objective: To provide information regarding the use of folic acid for the prevention of neural tube defects (NTDs) and other congenital anomalies, in order that physicians, midwives, nurses, and other health-care workers can assist in the education of women in the preconception phase of their health care.

Option: Folic acid supplementation is problematic, since 50% of pregnancies are unplanned and the health status of women may not be optimal.

Outcomes: Folic acid supplementation has been proven to decrease or minimize specific birth defects.

Evidence: A systematic review of the literature, including review and peer-reviewed articles, government publications, the previous Society of Obstetricians and Gynaecologists of Canada (SOGC) Policy Statement of March 1993, and statements from the American College of Obstetrics and Gynecology, was used to develop a new clinical practice guideline for the SOGC.

Values: Peer-review process within the committee structure.

Benefits, harms, and costs: The benefit is reduced lethal and severe morbidity birth defects and the harm is minimal. The personal cost is of vitamin supplementation on a daily basis and eating a healthy diet.

Recommendations:
1. Women in the reproductive age group should be advised about the benefits of folic acid supplementation during well-visit births (birth control renewal, Pap testing, yearly examination), especially if pregnancy is contemplated. (III-A)
2. Women should be advised to maintain a healthy nutritional diet, as recommended in Canada’s Food Guide to Healthy Eating (good or excellent sources of folic acid: broccoli, spinach, peas, Brussels sprouts, corn, beans, lentils, oranges). (II-1A)
3. Women who could become pregnant should be advised to take a multivitamin containing 0.4 mg to 1.0 mg of folic acid daily. (II-1A)
4. Women taking a multivitamin with folic acid supplement should be advised not to take more than 1 daily dose of vitamin supplement, as indicated on the product label. (II-2A)
5. Women in intermediate- to high-risk categories for NTDs (NTD-affected previous pregnancy, family history, insulin-dependent diabetes, epilepsy treatment with valproic acid or carbamazepine) should be advised that high-dose folic acid (4.0 mg–5.0 mg daily) supplementation is recommended. This should be taken as folic acid alone, not in a multivitamin format, due to risk of excessive intake of other vitamins such as vitamin A. (I-A)
6. The choice of a 5 mg folic acid daily dose for women considering a pregnancy should be made under medical supervision after minimizing the risk of undiagnosed vitamin B12 deficiency (hypersegmentation of polymorphonuclear cells, macrocytic indices, large ovalocytes, leukopenia, thrombocytopenia, markedly elevated lactate dehydrogenase level, confirmed red blood cell folate level). (II-2A)
7. Signs or symptoms of vitamin B12 deficiency should be considered before initiating folic acid supplementation of doses greater than 1.0 mg. (III-A)
8. A three-generation pedigree on the families of both the pregnant woman and the biological father should be obtained to...
identify increased risk for congenital birth defects (i.e., NTD, cardiac, chromosomal, genetic). (III-A)

9. Women who become pregnant should be advised of the availability of noninvasive screening tests and invasive diagnostic tests for congenital birth defects (including NTDs): maternal serum “triple marker screen” at 15 to 20 weeks, ultrasound at 16 to 20 weeks, and amniocentesis after 15 weeks of pregnancy if a positive screening test is present. (I-A)

**Validation:** This is a revision of a previous guideline and information from other consensus reviews from medical and government publications has been used.

**Sponsor:** The Society of Obstetricians and Gynaecologists of Canada.


**INTRODUCTION**

It is estimated that at least 5% of babies are born with some serious congenital anomaly.1 Of these 5 babies in 100, 2 or 3 will have anomalies that can be recognized prenatally by a noninvasive screening test, through invasive diagnostic testing, or at birth, while the other 2 babies will have developmental or functional anomalies recognized during the first year of their life.1 The ingestion of folic acid by a woman prior to conception and during the early stages of pregnancy plays a role in preventing neural tube defects (NTDs) and has been associated with preventing other congenital anomalies.2 Public health initiatives to increase the awareness and prevention of birth defects have focused on folic acid intake for the prevention of NTDs, but there are several studies that have indicated that taking multiple vitamins containing folic acid during the periconception period can reduce the risk of other neonatal conditions such as congenital heart defects,5 urinary tract anomalies5,6 oral facial clefts,2,7-9 limb defects,2 and pyloric stenosis.3 It has been estimated that as many as half of all birth defects can be prevented if women of childbearing age consume an adequate amount of folic acid, either by eating sufficient quantities of foods that are fortified with folic acid or by taking vitamin supplements.10

The objective of this clinical practice guideline update is to inform women’s health-care providers of new information regarding the use of folic acid for the prevention of neural tube defects and other congenital anomalies. The quality of evidence reported in this guideline has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination (Table 1).11

**METHODS**

A systematic review of the literature, including review and peer-reviewed articles, government publications, the previous Society of Obstetricians and Gynaecologists of Canada (SOGC) Policy Statement *The Use of Folic Acid for Prevention of Neural Tube Defects* published in March 1993,12 and statements from the American College of Obstetrics and Gynecology,13 was used to develop a new clinical practice guideline for the SOGC.

<table>
<thead>
<tr>
<th>TABLE 1 QUALITY OF EVIDENCE ASSESSMENT11</th>
<th>CLASSIFICATION OF RECOMMENDATIONS11</th>
</tr>
</thead>
<tbody>
<tr>
<td>The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination.</td>
<td>Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Canadian Task Force on the Periodic Health Examination.</td>
</tr>
<tr>
<td>I: Evidence obtained from at least one properly randomized controlled trial.</td>
<td>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</td>
</tr>
<tr>
<td>II-1: Evidence from well-designed controlled trials without randomization.</td>
<td>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</td>
</tr>
<tr>
<td>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</td>
<td>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</td>
</tr>
<tr>
<td>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</td>
<td>D. There is fair evidence to support the recommendation that the condition be not considered in a periodic health examination.</td>
</tr>
<tr>
<td>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</td>
<td>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</td>
</tr>
</tbody>
</table>

RESULTS

NEURAL TUBE DEFECTS

INCIDENCES AND INHERITANCE
Neural tube defects are severe birth anomalies, due to the lack of neural tube closure at either the upper or lower end in the third to fourth week after conception (day 26 to day 28 post-conception).14 The incidence and the empiric recurrence risk for NTDs vary across North American regions (Table 2).10,14-22

In Canada, the birth prevalence of NTDs has declined from a rate of 11.6 per 10 000 live births in 1989 to 7.5 per 10 000 total births (live births and stillbirths) in 1997.23 Reasons given for this decrease in the rate of NTDs include an increased usage of prenatal diagnoses (ultrasound, maternal serum screening) with subsequent pregnancy termination and, possibly, increased vitamin supplementation.23 The rate of NTDs tends to be higher in Eastern Canada than in Western Canada.24,25 Women of certain ethnic groups including Celtic26 and Sikh,27 as well as women from Northern China,28 are at higher risks of having children with NTDs.24-28 It remains unclear whether these risks vary due to genetic predisposition, culture dietary preferences, or a combination of these factors.

Multifactorial inheritance24,29,30 is the most common cause of NTDs, but monogenic, chromosomal, and teratogenic causes have specific risks and have not been studied in association with folic acid deprivation or supplementation (Table 3).14 The prevalence of aneuploidy and additional anatomical abnormalities in fetuses with open spina bifida was reviewed using Utah birth defect network data.31 Chromosome results were known in 45 of 51 cases of open spina bifida, with 6 cases (13%) having aneuploidy.

TABLE 2
INCIDENCE AND RECURRENCE RISK FOR NTD IN DIFFERENT REGIONS OF CANADA AND THE UNITED STATES1,10,19-22

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence (per 1000 total births)</th>
<th>Recurrence Risks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Ontario</td>
<td>1.2 (1986)</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>1.6 (1995)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9 (1999)</td>
<td></td>
</tr>
<tr>
<td>Quebec</td>
<td>4.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>United States</td>
<td>1.4–1.6</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Canada</td>
<td>0.75 (1997)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3
RECOGNIZED CONDITIONS ASSOCIATED WITH NEURAL TUBE DEFECTS14*

1. Multifactorial: Homocysteine metabolism variants (MTHFR)
2. Monogenic: AR Acrocallosal syndrome
   Cerebro-costo-mandibular syndrome
   Fanconi’s pancytopenia syndrome
   Fraser’s syndrome
   Hydroethalysus syndrome
   Jarcho-Levin syndrome
   Meckel-Gruber syndrome
   AD Waardenburg’s syndrome
3. Chromosomal: Miller-Dieker syndrome (deletion 17p13.3)
   Triploidy
   Trisomy 9 (mosaic)
   Trisomy 13
   Trisomy 18
4. Teratogen: Fetal hyperthermia spectrum
   Fetal alcohol syndrome
   Fetal amniopterin/methotrexate syndrome
   Fetal rubella
   Fetal valproate/carbamazepine/maternal epilepsy syndrome
   Maternal insulin-dependent diabetes (preconception)
5. Unknown: Caudal dysplasia sequence
   Child syndrome
   Extrophy of cloacae sequence
   Laterality sequences
   Limb-body Wall complex
   Monozygotic twinning

*NTD: neural tube defect; MTHFR: 5,10-methylenetetra-hydrofolate reductase; AR: autosomal recessive inheritance; AD: autosomal dominant inheritance.
only reduce the risk of NTDs. Women at increased risk for a pregnancy complicated by NTDs often have a history of:

- a previous fetus or child with an NTD
- a first-, second-, or third-degree relation with an NTD
- insulin-dependent (type 1) diabetes
- epilepsy and the ingestion of valproic acid or carbamazepine for seizure control
- use of folic acid antagonists (amniopterin, methotrexate)

Noninvasive prenatal diagnoses by ultrasound and maternal serum screening should be offered at 16 to 20 weeks’ and 15 to 20 weeks’ gestation, respectively, and will identify 95% to 100% of NTDs (anencephaly, 100%; spina bifida, 95%). Ultrason sound imaging of the cranium and the identification of cranial scalloping (lemon sign) and cerebellar crowding (banana sign) in association with mild ventriculomegaly is diagnostic of an open myelomeningocele, even if a defect is not easily identifiable in the spine due to the level of the spinal defect, fetal position, or maternal habitus. After 15 weeks of pregnancy, invasive prenatal diagnosis with ultrasound-guided amniocentesis, with confirmation by increased levels of amniotic fluid alphafetoprotein and acetycholinesterase, can be diagnostic of open or closed lesions, and used to evaluate fetal karyotype.

FOLIC ACID AND PREVENTION

A recent Health Canada document entitled *Preconception Health: Folic Acid for Primary Prevention of Neural Tube Defects – a Resource Document for Health Professionals 2002*, states that, from the human data, it is clear that periconceptional use of supplements containing folic acid substantially reduces the risks of occurrence (first affected pregnancy) and recurrence (additional affected pregnancies) of neural tube defects.

Women should be advised to maintain a healthy nutritional diet as recommended in *Canada’s Food Guide to Healthy Eating*. Good or excellent sources of folic acid are found in broccoli, spinach, peas, Brussels sprouts, corn, lentils, and oranges.

A randomized trial for the prevention of primary occurrence found periconceptional vitamin supplementation (12 vitamins including 0.8 mg of folic acid, 4 minerals, 3 trace elements) decreased the incidence of a first occurrence of an NTD. Previous case control studies had provided supportive and equivocal evidence that pregnant women using multivitamins containing folic acid or dietary folic acid had a lower risk of occurrence of NTDs than women not taking supplements.

For prevention of recurrence of NTDs, a randomized double-blind clinical trial, involving 1195 completed pregnancies in high-risk women from 33 centres, reported 72% fewer cases of NTDs among the children of the folic acid supplementation group than among the offspring of controls who did not take folic acid supplementation. The recurrence rate decreased from 3.5% to 1% for women randomized to receive 4 mg folic acid supplementation prior to pregnancy and throughout the first 6 weeks of pregnancy. The results in the group taking vitamins without folic acid were similar to the results in the group not taking vitamin supplementation, with recurrence risks of 3.5%.

Wald *et al.* looked at the dose of folic acid to maximize the already known benefit of folic acid in preventing NTDs. The study analyzed published data from 13 other studies of folic acid supplementation on serum folate concentrations, as well as results from a large cohort study of the risk of NTDs according to serum folate. The results of the analysis indicated that the folic acid preventive effect is greater in women with an initial low serum folate concentration than in women with higher serum folate concentrations. The results of serum folate levels have also been used to predict direct observations from large randomized trials on the effect of food fortification in preventing NTDs. For Caucasian women, a serum folate of 5 ng/mL, about 0.2 mg per day (the United States’ level of folic acid fortification) would be expected to reduce NTDs by about 20%. A similar effect can be expected from the current British fortification recommendation of 0.24 mg per day. An increase of 0.4 mg/day would reduce the risk by about 36%, 1 mg per day by 57%, and the use of a 5 mg tablet daily would reduce risk by about 85%. Wald *et al.* concluded that folic acid fortification levels should be increased accordingly, and that women planning a pregnancy should take 5 mg folic acid tablets daily instead of the 0.4 mg dose presently recommended. Subsequent letters to the editor showed support for the concept while others recommended caution.

The choice of a 5 mg folic acid daily dose for Canadian women considering a pregnancy should be made under medical supervision after minimizing the risk of undiagnosed vitamin B12 deficiency.

FOLIC ACID SUPPLEMENTATION AND BIRTH DEFECTS OTHER THAN NEURAL TUBE DEFECTS

Folic acid supplementation has been shown to benefit other congenital anomalies, such as congenital heart defects, urinary tract anomalies, oral facial clefts, limb defects, and pyloric stenosis. A recent review summarizes the recent literature regarding prevention of congenital anomalies with periconceptional folic acid supplementation.

POTENTIAL HARM OF EXCESS FOLIC ACID INTAKE

Folic acid, in the recommended dosage of 0.4 to 1.0 mg, is not known to cause demonstrable harm to the developing fetus or the pregnant woman. Folic acid is water soluble and its excess is excreted through the urinary tract. The effects of higher intake of folic acid (i.e., >1 mg) are not well known, but they include masking the diagnosis of vitamin B12 deficiency. This concern has led to a recommendation that, for healthy women,
1 mg of folic acid daily (from either folic acid supplements or fortified foods) be considered the maximum dose.\textsuperscript{12,13} Folic acid can mask vitamin B\textsubscript{12} deficiency by correcting the mesoblastic anemia changes normally identifiable, but it does not prevent the neurological complications of vitamin B\textsubscript{12} deficiency. In fact, there has been some concern that high doses of folic acid may precipitate or exacerbate neurological symptoms of vitamin B\textsubscript{12} deficiency.\textsuperscript{50-53} Clinical symptoms of vitamin B\textsubscript{12} deficiency include tiredness, fatigue, chronic malaise, sore tongue, ataxic gait, and numbness of the fingers.\textsuperscript{55} Women with signs of red cracked tongue, peripheral neuropathy, ataxia, pallor, and other signs of anemia, and those given a dose of folic acid greater than 1 mg per day, should be investigated for possible vitamin B\textsubscript{12} deficiency.\textsuperscript{55} Other hematological characteristics\textsuperscript{55} of vitamin B\textsubscript{12} deficiency include hypersegmentation of polymorphonuclear cells, macrocystic indices, large ovalocytes, leukopenia, and thrombocytopenia. A markedly elevated lactate dehydrogenase level and red blood cell folate level are also usually observed.\textsuperscript{55}

Folic acid rarely has allergic responses but these may include erythema, rash, itching, general malaise, and bronchospasm.\textsuperscript{56}

INTERACTION OF DRUGS WITH FOLIC ACID

Serum folic acid levels may be affected by the metabolism of other medications, including antineoplastic agents, epileptic medications, oral contraceptives, and other medications (Table 4).\textsuperscript{12,13,40} Folic acid has recognized drug interactions\textsuperscript{57} with other commonly used medications such as hypertensive/thiazide combinations, digoxin, thyroid hormones, tetracycline, and thiazide diuretics.

VITAMINS AND MINERALS

There is strong evidence that the use of a multivitamin–multimineral supplement containing folic acid at 0.4 mg per daily dose reduces the risk of a first-occurrence NTD.\textsuperscript{40} The combination of ingredients varies greatly in over-the-counter preparations. It is suggested that multivitamin–multimineral preparations with 0.4 mg–1.0 mg of folic acid per daily dose be taken,\textsuperscript{40} but that mineral supplementation may not be necessary, due to the low risk of deficiency in Canada.\textsuperscript{40} Supplements containing herbs and other “nonmedicinal ingredients” should be avoided, as they have neither been proven to have any benefit nor been studied regarding harm.

Multivitamins should have vitamin A as beta-carotene rather than as retinol. Excess retinol (10 000 IU; 3300 RE) on a daily basis may cause birth defects.\textsuperscript{58} For this reason, women should not take more than 1 daily dose, as indicated on the product label.

FOLIC ACID FOOD FORTIFICATION

In Canada since 1998, in an effort to reduce the rate of NTDs, there has been mandatory fortification of white flour, enriched pasta, and cornmeal with folic acid. The overall benefit of fortification in reducing NTDs is yet to be determined.\textsuperscript{40,59} The minimal effective dose is also unknown.\textsuperscript{40,59}

CONCLUSION

Folic acid (through diet and supplementation) has been proven to decrease or minimize specific birth defects including neural tube defects, congenital heart disease, urinary tract anomalies, oral facial clefts, limb defects, and pyloric stenosis.\textsuperscript{2-9} Preconceptional folic acid supplementation should be recommended to women who may become pregnant. The dose of folic acid supplementation should be adjusted according to the patient’s history and needs.

RECOMMENDATIONS

1. Women in the reproductive age group should be advised about the benefits of folic acid supplementation during wellness visits (birth control renewal, Pap testing, yearly examination), especially if pregnancy is contemplated. (III-A)

2. Women should be advised to maintain a healthy nutritional diet, as recommended in Canada’s Food Guide to Healthy Eating (good or excellent sources of folic acid: broccoli, spinach, peas, Brussels sprouts, corn, beans, lentils, oranges). (III-A)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Effect</th>
<th>Mechanism</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Reduced folic acid effect</td>
<td>Interference with erythrocyte maturation</td>
<td>Caution</td>
</tr>
<tr>
<td>Phenobarbital, phenytoin, primidone</td>
<td>Reduced folic acid levels</td>
<td>Increased folic acid metabolism</td>
<td>Caution</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Loss of seizure control; decreased phenytoin levels</td>
<td>Increased phenytoin metabolism</td>
<td>Monitor phenytoin levels</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Decreased folic acid levels</td>
<td>Impaired absorption</td>
<td>Caution</td>
</tr>
</tbody>
</table>
3. Women who could become pregnant should be advised to take a multivitamin containing 0.4 mg to 1.0 mg of folic acid daily. (II-1A)

4. Women taking a multivitamin with folic acid supplement should be advised not to take more than 1 daily dose of vitamin supplement, as indicated on the product label. (II-2A)

5. Women in intermediate- to high-risk categories for NTDs (NTD-affected previous pregnancy, family history, insulin-dependent diabetes, epilepsy treatment with valproic acid or carbamazepine) should be advised that high-dose folic acid (4.0 mg–5.0 mg daily) supplementation is recommended. This should be taken as folic acid alone, not in a multivitamin format, due to risk of excessive intake of other vitamins such as vitamin A. (I-A)

6. The choice of a 5 mg folic acid daily dose for women considering a pregnancy should be made under medical supervision after minimizing the risk of undiagnosed vitamin B12 deficiency (hypermegmentation of polymorphonuclear cells, macrocytic indices, large ovalocytes, leukopenia, thrombocytopenia, markedly elevated lactate dehydrogenase level, confirmed red blood cell folate level). (II-2A)

7. Signs or symptoms of vitamin B12 deficiency should be considered before initiating folic acid supplementation of doses greater than 1.0 mg. (III-A)

8. A three-generation pedigree on the families of both the pregnant woman and the biological father should be obtained to identify increased risk for congenital birth defects (i.e., NTD, cardiac, chromosomal, genetic). (III-A)

9. Women who become pregnant should be advised of the availability of noninvasive screening tests and invasive diagnostic tests for congenital birth defects (including NTDs): maternal serum “triple marker screen” at 15 to 20 weeks, ultrasound at 16 to 20 weeks, and amniocentesis after 15 weeks of pregnancy if a positive screening test is present. (I-A)

REFERENCES


