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Pre-conceptional Vitamin/Folic Acid Supplementation 2007: The Use of Folic Acid in Combination With a Multivitamin Supplement for the Prevention of Neural Tube Defects and Other Congenital Anomalies

This guideline was prepared by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada and The Motherisk Program, The Hospital for Sick Children Toronto, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To provide information regarding the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies, so that physicians, midwives, nurses, and other health care workers can assist in the education of women in the pre-conception phase of their health care.

Option: Supplementation with folic acid and vitamins is problematic, since 50% of pregnancies are unplanned, and women's health status may not be optimal when they conceive.

Outcomes: Folic acid in combination with a multivitamin supplement has been associated with a decrease in specific birth defects.

Evidence: Medline, PubMed, and Cochrane Database were searched for relevant English language articles published between 1985 and 2007. The previous Society of Obstetricians and Gynaecologists of Canada (SOGC) Policy Statement of November 1993 and statements from the American College of Obstetrics and Gynecology and Canadian College of Medical Geneticists were also reviewed in developing this clinical practice guideline.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care.

Benefits, Harms, and Costs: Promoting the use of folic acid and a multivitamin supplement among women of reproductive age will reduce the incidence of birth defects. The costs are those of daily vitamin supplementation and eating a healthy diet.

Recommendations

1. Women in the reproductive age group should be advised about the benefits of folic acid in addition to a multivitamin supplement 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 diet, as recommended in *Eating Well With Canada's Food Guide (Health Canada).* Foods containing excellent to good sources of folic acid are fortified grains, spinach, lentils, chick peas, asparagus,

broccoli, peas, Brussels sprouts, corn, and oranges. However, it is unlikely that diet alone can provide levels similar to folate-multivitamin supplementation. (III-A)

3. Women taking a multivitamin containing folic acid should be advised *not* to take more than *one daily dose* of vitamin supplement, as indicated on the product label. (II-2-A)
4. Folic acid and multivitamin supplements should be widely available without financial or other barriers for women planning pregnancy to ensure the extra level of supplementation. (III-B)
5. Folic acid 5 mg supplementation will not mask vitamin B_{12} deficiency (pernicious anemia), and investigations (examination or laboratory) are not required prior to initiating supplementation. (II-2-A)
6. The recommended strategy to prevent *recurrence* of a congenital anomaly (anencephaly, myelomeningocele, meningocele, oral facial cleft, structural heart disease, limb defect, urinary tract anomaly, hydrocephalus) that has been reported to have a decreased incidence following preconception / first trimester folic acid +/- multivitamin oral supplementation is planned pregnancy +/- supplementation compliance. A folate-supplemented diet with additional daily supplementation of multivitamins with 5 mg folic acid should begin at least three months before conception and continue until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4–6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4–1.0 mg). (I-A)
7. The recommended strategy(ies) for primary prevention or to decrease the incidence of fetal congenital anomalies will include a number of options or treatment approaches depending on patient age, ethnicity, compliance, and genetic congenital anomaly risk status.
   - **Option A:** Patients with no personal health risks, planned pregnancy, and good compliance require a good diet of folate-rich foods and daily supplementation with a multivitamin with folic acid (0.4–1.0 mg) for at least two to three months before conception and throughout pregnancy and the postpartum period (4–6 weeks and as long as breastfeeding continues). (II-2-A)
   - **Option B:** Patients with health risks, including epilepsy, insulin dependent diabetes, obesity with BMI >35 kg/m^2, family history of neural tube defect, belonging to a high-risk ethnic group (e.g., Sikh) require increased dietary intake of folate-rich foods and daily supplementation, with multivitamins with 5 mg folic acid, beginning at least three months before conception and continuing until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4–6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4–1.0 mg). (II-2-A)
   - **Option C:** Patients who have a history of poor compliance with medications and additional lifestyle issues of variable diet, no consistent birth control, and possible teratogenic substance use (alcohol, tobacco, recreational non-prescription drugs) require counselling about the prevention of birth defects and health problems with folic acid and multivitamin supplementation. The higher dose folic acid strategy (5 mg) with multivitamin should be used, as it may obtain a more adequate serum red blood cell folate level with irregular vitamin / folic acid intake but with a minimal additional health risk. (III-B)
8. The Canadian Federal Government could consider an evaluation process for the benefit/risk of increasing the level of national folic acid flour fortification to 300 mg/100 g (present level 140 mg/100 g). (III-B)
9. The Canadian Federal Government could consider an evaluation process for the benefit/risk of additional flour fortification with multivitamins other than folic acid. (III-B)
10. The Society of Obstetricians and Gynaecologists of Canada will explore the possibility of a Canadian Consensus conference on the use of folic acid and multivitamins for the primary prevention of specific congenital anomalies. The conference would include Health Canada/Congenital Anomalies Surveillance, Canadian College of Medical Geneticists, Canadian Paediatric Society, Motherisk, and pharmaceutical industry representatives.

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.

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ABBREVIATIONS

AD	autosomal dominant inheritance
AR	autosomal recessive inheritance
BMI	body mass index
CI	confidence interval
MTHFR	5.10-methylenetetrahydrofolate reductase
NTD	neural tube defect
RBC	red blood cell
RCT	randomized controlled trial

INTRODUCTION

It is estimated that at least 5% of babies are born with some serious congenital anomaly[1]; 2% to 3% will have anomalies that can be recognized prenatally by non-invasive screening test, through invasive diagnostic testing, or at birth, and 2% will have developmental or functional anomalies recognized during the first year of life.[1] Folic acid ingested prior to conception and during the early stages of pregnancy plays a role in preventing neural tube defects and has been associated with preventing other congenital anomalies.[2] Folic acid helps produce and maintain new cells; it is important during times of rapid cell division and growth (i.e., embryonic and fetal periods). Public health initiatives to increase the awareness and prevention of birth defects have focused on folic acid intake for the prevention of NTDs, but several studies have indicated that taking multivitamins containing folic acid during the periconception period can reduce the risk of other conditions such as heart defects,[2–5] urinary tract anomalies,[5,6] 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 food that are fortified with folic acid or by taking vitamin supplements.[10–12] The objective of this clinical practice

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
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	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[13]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[13]

guideline update is to give women's health care providers new data/information about the use of folic acid with a multivitamin supplement 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 of the Canadian Task Force on Preventive Health Care (Table 1).[13]

Peer-reviewed articles, government publications (Health Canada, Preconception Health 2002[14]; NIH Clinical Center, Office of Dietary Supplements 2005),[15] the 2003 Society of Obstetricians and Gynaecologists of Canada (SOGC) Policy Statement, The Use of Folic Acid for Prevention of Neural Tube Defects,[16] and statements from The American College of Obstetrics and Gynecology[17] and Canadian College of Medical Geneticists,[18] were reviewed in developing this guideline.

NEURAL TUBE DEFECTS: INCIDENCE AND INHERITANCE

Neural tube defects are severe birth anomalies that occurs because of a 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).[19] The incidence (0.5–4.0/1000 births) of NTDs varies across North American regions and a decreasing incidence (1.58 per 1000 births to 0.86 per 1000 births) is shown with folic acid supplementation.[20] Recurrence risks reflect the genetic contribution in different regions, but an estimated 1% recurrence with folic acid prophylaxis is given.[1,10,17,20–29]

In Canada, the birth prevalence of NTDs has declined from a rate of 10.0 per 10 000 live births in 1991 to 5.8 per 10 000 total births (live births and stillbirths) in 1999.[28] Reasons given for this decrease in the rate of NTDs include an increased use of tests (ultrasound, maternal serum screening) and subsequent pregnancy termination, the fortification of food with folic acid, and increased vitamin supplementation.[28] The rate of NTDs tends to be higher in Eastern Canada than in Western Canada.[30,31] Women of certain ethnic groups, including Celtic[32] and Sikh,[33] as well as women from Northern China,[34] are at a higher risk of having children with NTDs.[30–34] It remains unclear whether these risks vary because of genetic predisposition, cultural dietary preferences, or a combination of these factors.

Multifactorial inheritance[30,35,36] is the most common cause of NTDs, but monogenic, chromosomal, and teratogenic causes have specific effects that have not been studied in association with folic acid deprivation or supplementation (Table 2).[19] The prevalence of aneuploidy and additional anatomical abnormalities in fetuses with open spina bifida was reviewed using Utah Birth Defect Network data.[37] Chromosome results were known in 45 of 51 cases of open spina bifida, with six cases (13%) of aneuploidy. Additional major anatomic abnormalities were present in four of the six cases and included cardiac, renal, omphalocele, brain,

Table 2. Recognized conditions associated with neural tube defects[19]

1. Multifactorial	Homocysteine metabolism variants (MTHFR)
2. Monogenic	AR Acrocallosal syndrome
	Cerebro-costo-mandibular syndrome
	Fanconi's pancytopenia syndrome
	Fraser's syndrome
	Hydrolethalus 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
	CHILD syndrome (mutation NSDHL gene X q 28)
4. Teratogen	Fetal hyperthermia spectrum
	Fetal alcohol syndrome
	Fetal amineopterin/methotrexate syndrome
	Fetal rubella
	Fetal valproate/carbamazepine/maternal epilepsy syndrome
	Maternal pre-existing diabetes (pre-conception)
5. Unknown Etiology	Caudal dysplasia sequence
	Extrophy of cloaca sequence
	Laterality sequences
	Limb-body wall complex
	Monozygotic twinning

and bilateral oral clefting. There was a 4% risk of aneuploidy in sonographically isolated spina bifida cases within this population.[37]

PRENATAL DIAGNOSIS

All pregnant women should be offered routine screening for NTDs with specific and appropriate timing.[38–44] Folic acid supplementation will not eliminate but will reduce the risk of NTDs.[45] Women with an increased risk for a pregnancy complicated by NTDs often have a history of

- a previous fetus or child with an NTD[16,17,43,46]
- a first-, second-, or third-degree relation with an NTD[16,43,46]
- pre-existing maternal diabetes as well as insulin-dependent (type 1) diabetes[16,43,46]
- epilepsy and the ingestion of valproic acid or carbamazepine for seizure control[16,43,46]
- use of folic acid antagonists (amniopterin, methotrexate)[16,43,46]

Non-invasive prenatal diagnostic testing by ultrasound and maternal serum screening,[44] which should be offered at 16 to 20 weeks' gestation and 15 to 20 weeks' gestation, respectively, will identify 95% to 100% of NTDs (anencephaly, 100%; spina bifida, 95%). Ultrasound imaging[47,48] 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 if, even with improved ultrasound technique and resolution, a defect is not easily identifiable in the spine because of the level of the spinal defect, fetal position, or maternal habitus. After 15 weeks of pregnancy, invasive prenatal diagnostic testing with ultrasound-guided amniocentesis can evaluate the fetal karyotype and measure amniotic fluid alpha fetoprotein and acetylcholinesterase to assist in differentiating between open or closed lesions.[44]

FOLIC ACID AND PREVENTION

A Health Canada document,[14] *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. Similar summary information is available from the National Institutes of Health Clinical Center document, *Dietary Supplement Fact Sheet: Folate 2005*.[15]

Women should be advised to maintain a healthy diet, as recommended in *Eating Well With Canada's Food Guide* (Health Canada).[49] Good or excellent sources of folic acid include broccoli, spinach, peas, Brussels sprouts, corn, lentils, and oranges.

A randomized trial[50] 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 NTD. Previous case–control studies had provided supportive or equivocal evidence that pregnant women using multivitamins containing folic acid or dietary folic acid had a lower risk of occurrence NTDs than women not taking supplements.[51–55]

With respect to prevention of recurrence of NTDs, a randomized double-blind clinical trial[45] involving 1195 completed high-risk pregnancies women from 33 centres reported 72% fewer cases of NTDs among the offspring of the folic acid supplementation group than among the offspring of controls who did not take folic acid supplementation.[45] 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 six 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.[56] evaluated the dose of folic acid required to maximize the already known benefit of folic acid in preventing NTDs. The study analyzed published data from 13 studies of folic acid supplementation on serum folate concentrations, as well as results from a large cohort study on the risk of NTDs according to serum folate.

> Such results predict that the preventive effect is greater in women with low serum folate than in those with higher concentrations. The results have also been used to predict direct observations from large randomised trials and the effect of food fortification. From a typical western background serum folate of 5 ng/mL, about 0.2 mg/day (the US level of folic acid fortification) would be expected to reduce NTDs by about 20%; a similar effect can be expected from the current British recommendation (0.24 mg/day). An increase of 0.4 mg/day would reduce risk by about 36%, of 1 mg/day by 57%, and taking a 5-mg tablet daily would reduce risk by about 85%.[56]

Wald et al.[56] 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 currently recommended. Some of the subsequent letters to the editor showed support [57,58] for the concept, although others recommended caution.[59] This increased dosage of folic acid has not yet been widely implemented for preconception populations.

Folic acid supplementation reduces NTDs,[60–66] but new data (2006) for Ontario analyzed by Motherisk indicated that 40% of females in the reproductive age had RBC folate below 900 nmol/L and half of these (20%) were below 700 nmol/L, with 900 nmol/L or greater being necessary for maximum protection against NTDs. On the basis of this information, it can be estimated that 200 000 pregnant Canadian women are suboptimally protected against NTD each year.[67] Other investigators have indicated that women attempting pregnancy will achieve a level of 900 nmol/L with a supplementation dosage of 0.4 mg folic acid.[68] Additional information indicates that only 28% of Canadian women took folic acid or a multivitamin containing folic acid and that supplementation was not used the same way/to the same extent in all ethnic groups.[69] Other strategies have been proposed to influence and improve folic acid supplementation.[70–72]

FOLIC ACID AND VITAMIN SUPPLEMENTATION AND BIRTH DEFECTS OTHER THAN NEURAL TUBE DEFECTS

Folic acid in combination with multivitamin supplements has been shown to reduce other congenital anomalies, such as heart defects,[2–5] urinary tract anomalies,[5–6] oral facial clefts,[33–35, 73,74] limb defects,[2] and pyloric stenosis.[3]

A recent review has analyzed the published literature regarding the prevention of congenital anomalies with periconceptional folic acid supplementation.[75] Meta-analysis of prenatal multivitamin supplementation containing folic acid and the rates of congenital anomalies has shown decreased risks for the following:

- NTD (OR case-control 0.67; [0.58–0.77] cohort/RCT 0.52[0.39–0.69])
- Cardiovascular defects (OR case-control 0.78; [0.67–0.92] cohort/RCT 0.61[0.40–0.92])
- Limb defects (OR case-control 0.48; [0.30–0.76] cohort/RCT 0.57[0.38–0.85])

Table 3. Interactions: Drugs and folic acid[14–17,46,63,84]

Drugs	DX	Effect	Mechanism	Importance
Chloramphenicol	cancer	reduced folic acid effect	interference with erythrocyte maturation	caution
Methotrexate	cancer arthritis	reduced folic acid effect		
Phenobarbital, phenytoin, primidone	epilepsy	reduced folic acid levels	increased folic acid metabolism	caution
Phenytoin	epilepsy	loss of seizure control; decreased phenytoin levels	increased phenytoin metabolism	monitor phenytoin levels
Sulfasalazine	Crohn's disease ulcerative colitis	decreased folic acid levels	impaired absorption	caution
Metformin	type II diabetes	reduced effect	increased glucose	caution
Triamterene	diuretic	_____	_____	NIH caution
Barbituates	sedation	_____	_____	NIH caution

- Cleft palate (OR case-control 0.76; [0.62–0.93] cohort/RCT 0.42 [0.06–2.84])
- Oral clefts with or without cleft palate (OR case-control 0.63; [0.54–0.73] cohort/RCT 0.58 [0.28–1.19])
- Urinary tract anomalies (OR case-control 0.48; [0.30–0.76] cohort/RCT 0.68[0.35–1.31])
- Congenital hydrocephalus (OR case-control 0.37; [0.24–0.56] cohort/RCT 1.54[0.53–4.50])

No effects were shown in preventing Down syndrome, pyloric stenosis, undescended testis, or hypospadias.[75] This meta-analysis is limited to studies with the combined multivitamin-folic acid treatment and excludes studies that did not report malformation rates, focused on folic acid alone, and did not contain a control group. Additional studies support these associations. [76,77]

Other pediatric benefits have been identified following prenatal multivitamin supplementation before and in early pregnancy.[78,79] Maternal use of prenatal multivitamins is associated with a decreased risk for pediatric brain tumours (OR 0.73, [0.60–0.88]), neuroblastoma (0.53, [0.42–0.68]), and leukemia (ALL) (OR 0.61, [0.50–0.74]).[78] It was stated that it is not known which constituent(s) among the multivitamins confers this protective effect.

MATERNAL ISSUE WITH FOLIC ACID FORTIFICATION

A debate entitled *Should Folic Acid Be Mandatory*[80] was recently published. The "yes" opinion states a clear benefit in preventing neural tube defects, with substantial evidence on safety and no valid indication of harm. The "no" opinion states that further investigation of the potential cancer promoting effects of exposure to folic acid in susceptible people is desirable before mandatory fortification starts. Folic acid has not been shown to promote breast cancer[81] or to prevent[82] it. Ovarian cancer studies[83] suggest (but not with statistical significance) that relatively high dietary folate intake may be associated with a reduction in ovarian cancer risk among woman with high alcohol and methionine intake.

FOLIC ACID METABOLISM

The risk of toxicity from folic acid intake from supplements and/or fortified foods is low. It is a water soluble vitamin, so any excess intake is usually excreted in urine.

Medical conditions that increase the need for folic acid or result in increased excretion of folic acid include pregnancy/lactation, alcohol abuse, malabsorption (gastric bypass patients may be at risk), renal dialysis, liver disease, and certain anemias.

Serum folate acid levels may be affected by the metabolism of other medications, including antineoplastic agents, epileptic medications, and other medications (Table 3).[14–17,46,84]

OTHER VITAMIN ISSUES

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.[85] For this reason, women should *not* take more than one daily dose, as indicated on the product label.

FOLIC ACID FOOD FORTIFICATION

In Canada since 1998, in an effort to try and reduce the rate of NTDs, there has been mandatory folic acid fortification of white flour, enriched pasta, and cornmeal. The overall benefit of fortification in reducing NTDs has been determined.[14,15,45,74–77,86] The most recent Canadian data have shown that the prevalence of neural tube defects decreased from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full fortification period (1998–2002), a 46% reduction (95% CI, 40–51). The decrease was greater for spina bifida than for anencephaly and encephalocele.[20]

POTENTIAL HARM OF FOLIC ACID INTAKE

Folic acid, in a 0.4 to 1.0 mg daily dose[12–15,46,87] is not known to cause demonstrable harm to the developing fetus or the pregnant woman. Folic acid is water soluble and excess is excreted through the urinary tract. Patients aged 50 years or over are at greater risk for vitamin B_{12} deficiency than younger women, but this is not the age group in which pregnancy usually occurs. A recent Australian study[88] found that high serum folate did not mask the macrocytosis of cobalamin deficiency of pernicious anemia. Macrocytosis appears to retain its value as a marker of cobalamin deficiency in people with serum folate concentrations above the population average. The folic acid dose of 5 mg has not been reported to have maternal or fetal risks.[55–63,89]

Folic acid and multivitamin supplementation is possibly associated with an increased incidence of twins.[12,90–92]

There are some concerns about folic acid supplementation being associated with an increased risk of neoplasia or possible exacerbation of pre-existing colorectal cancer. Increased rates for colorectal cancer have been observed since food fortification was introduced in Canada and United States. This effect has not been proven but needs to be acknowledged.[93]

This guideline recommends the use of folic acid in the perinatal period; the use of folic acid is therefore limited to usually recurrent 6- to 12-month time periods. Other long-term uses for folic acid in the clinical context (alcoholics, anemia, liver disease, kidney disease, malabsorption, cardiac disease, cancer treatment) are not discussed. Allergic responses to folic acid are rare, but may include erythema, rash, itching, general malaise, and bronchospasm.[94]

CURRENT SITUATION IN CANADA

In Canada, flour is fortified with folic acid. Its introduction coincided with an observed decrease in NTDs in liveborns,[20,95] but this may be related to prenatal diagnosis/termination rather than fortification alone.[96,97] Women who are motivated may be able to reach appropriate RBC folate levels with a selected diet, supplemented foods, and compliant daily oral folic acid supplementation (0.4–1.0 mg), but this situation may represent less than 15% to 20% of the pregnant population.

The combination of multivitamin and folic acid can be taken as oral supplementation or single combined pill (multivitamin with 0.4–1.0 mg or 5 mg) or as a multiple tablet option (multivitamin with 0.4–1.0 mg; for higher folic acid doses, add single 1 mg folic acid tablets as necessary). Oral supplementation may be variable because of compliance issues with daily oral tablet use (nausea, "forgot," "don't like to take pills").[98,99]

Conception data indicate that 50% of pregnancies are unplanned with no additional oral supplement (multivitamin with folic acid) being used. The options described below take this into consideration.

TREATMENT OPTIONS

Option A: Patients with no personal health risks, planned pregnancy, and good compliance require a good diet of folate-rich foods and daily supplementation with a multivitamin with folic acid (0.4–1.0 mg) for at least two to three months before conception and throughout pregnancy and the postpartum period (4–6 weeks and as long as breastfeeding continues). (II-2-A)

Option B: Patients with health risks, including epilepsy, insulin dependent diabetes, obesity with BMI > 35 kg/m^2, family history of neural tube defect, belonging to a high-risk ethnic group (e.g., Sikh) require increased dietary intake of folate-rich foods and daily supplementation, with multivitamins with 5 mg folic acid, beginning at least three months before conception and continuing until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4–6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4–1.0 mg). (II-2-A)

Option C: Patients who have a history of poor compliance with medications and additional lifestyle issues of variable diet, no consistent birth control, and possible teratogenic substance use (alcohol, tobacco, recreational non-prescription drugs) require counselling about the prevention of birth defects and health problems with folic acid and multivitamin supplementation. The higher dose folic acid strategy (5 mg) with multivitamin should be used, as it may obtain a more adequate serum red blood cell folate level with irregular vitamin / folic acid intake but with a minimal additional health risk. (III-B)

SUMMARY

Folic acid (in the diet and/or in a supplement)with a multivitamin has been proven to decrease or minimize specific birth defects including neural tube defects, congenital heart disease, urinary tract anomalies, oral facial clefts with or without cleft palate, limb defects, and hydrocephalus, as well as some pediatric cancers. The public health flour fortification initiative has been very beneficial with respect to primary prevention of birth defects. The recent comprehensive Canadian analysis of neural tube reduction after folic acid flour fortification has reported a 46% reduction. The observed reduction was greater for spina bifida (53%) than for anencephaly (38%) and encephalocele (31%). Further reductions in the incidence of congenital anomalies sensitive to folic acid and multivitamins should be possible with the participation of key stakeholders.

Recommendations

1. Women in the reproductive age group should be advised about the benefits of folic acid in addition to a multivitamin supplement 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 diet, as recommended in *Eating Well With Canada's Food Guide (Health Canada)*. Foods containing excellent to good sources of folic acid are fortified grains, spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn, and oranges. However, it is unlikely that diet alone can provide levels similar to folate-multivitamin supplementation. (III-A)
3. Women taking a multivitamin containing folic acid should be advised *not* to take more than *one daily dose* of vitamin supplement, as indicated on the product label. (II-2-A)
4. Folic acid and multivitamin supplements should be widely available without financial or other barriers for women planning pregnancy to ensure the extra level of supplementation. (III-B)
5. Folic acid 5 mg supplementation will not mask vitamin B_{12} deficiency (pernicious anemia), and investigations (examination or laboratory) are not required prior to initiating supplementation. (II-2-A)
6. The recommended strategy to prevent *recurrence* of a congenital anomaly (anencephaly, myelomeningocele, meningocele, oral facial cleft, structural heart disease, limb defect, urinary tract anomaly, hydrocephalus) that has been reported to have a decreased incidence following preconception / first trimester folic acid +/- multivitamin oral supplementation is planned pregnancy +/- supplementation compliance. A folate-supplemented diet with additional daily supplementation of multivitamins with 5 mg folic acid should begin at least three months before conception and continue until 10 to 12 weeks post conception. From 12 weeks post conception and continuing throughout pregnancy and the postpartum period (4–6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4–1.0 mg). (I-A)
7. The recommended strategy (ies) for primary prevention or to decrease the incidence of fetal congenital anomalies will include a number of options or treatment approaches depending on patient age, ethnicity, compliance, and genetic congenital anomaly risk status.
   - **Option A:** Patients with no personal health risks, planned pregnancy, and good compliance require a good diet of folate-rich foods and daily supplementation with a multivitamin with folic acid (0.4–1.0 mg) for at least two to three months before conception and throughout pregnancy and the postpartum period (4–6 weeks and as long as breastfeeding continues). (II-2-A)
   - **Option B:** Patients with health risks, including epilepsy, insulin dependent diabetes, obesity with BMI >35 kg/m^2, family history of neural tube defect, belonging to a high-risk ethnic group (e.g., Sikh) require increased dietary intake of folate-rich foods and daily supplementation, with multivitamins with 5 mg folic acid, beginning at least three months before conception and continuing until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4–6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4–1.0 mg). (II-2-A)
   - **Option C:** Patients who have a history of poor compliance with medications and additional lifestyle issues of variable diet, no consistent birth control, and possible teratogenic substance use (alcohol, tobacco, recreational non-prescription drugs) require counselling about the prevention of birth defects and health problems with folic acid and multivitamin supplementation. The higher dose folic acid strategy (5 mg) with multivitamin should be used, as it may obtain a more adequate serum red blood cell folate level with irregular vitamin / folic acid intake but with a minimal additional health risk. (III-B)
8. The Canadian Federal Government could consider an evaluation process for the benefit/risk of increasing the level of national folic acid flour fortification to 300 mg/100 g (present level 140 mg/100 g). (III-B)

9. The Canadian Federal Government could consider an evaluation process for the benefit/risk of additional flour fortification with multivitamins other than folic acid. (III-B)

10. The Society of Obstetricians and Gynaecologists of Canada will explore the possibility of a Canadian Consensus conference on the use of folic acid and multivitamins for the primary prevention of specific congenital anomalies. The conference would include Health Canada/Congenital Anomalies Surveillance, Canadian College of Medical Geneticists, Canadian Paediatric Society, Motherisk, and pharmaceutical industry representatives.

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