

# Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies

This Clinical Practice Guideline was prepared by the Genetics Committee, reviewed by the Family Physician Advisory Committee, and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure statements have been received from all contributors.

## Abstract

**Objective:** To provide updated information on the pre- and post-conception use of oral folic acid with or without a multivitamin/micronutrient supplement for the prevention of neural tube defects and other congenital anomalies. This will help physicians, midwives, nurses, and other health care workers to assist in the education of women about the proper use and dosage of folic acid/multivitamin supplementation before and during pregnancy.

**Evidence:** Published literature was retrieved through searches of PubMed, Medline, CINAHL, and the Cochrane Library in January 2011 using appropriate controlled vocabulary and key words (e.g., folic acid, prenatal multivitamins, folate sensitive birth defects, congenital anomaly risk reduction, pre-conception counselling). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English from 1985 and June 2014. Searches were updated on a regular basis and incorporated in the guideline to June 2014. Grey (unpublished) literature was identified through searching the

J Obstet Gynaecol Can 2015;37(6):534–549

**Key Words:** Folic acid, folate, prenatal multivitamins, micronutrients, neural tube defect, spina bifida, myelomeningocele, congenital anomalies, fetal anomalies, folate sensitive birth defects, congenital anomaly risk reduction, preconception counseling, birth defects, pregnancy, prevention

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**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
	L. 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 here has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.<sup>193</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.<sup>193</sup>

websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

**Costs, risks, and benefits:** The financial costs are those of daily vitamin supplementation and eating a healthy folate-enriched diet. The risks are of a reported association of dietary folic acid supplementation with fetal epigenetic modifications and with an increased likelihood of a twin pregnancy. These associations may require consideration before initiating folic acid supplementation. The benefit of folic acid oral supplementation or dietary folate intake combined with a multivitamin/micronutrient supplement is an associated decrease in neural tube defects and perhaps in other specific birth defects and obstetrical complications.

**Values:** The quality of evidence in the document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

### Summary Statement

In Canada multivitamin tablets with folic acid are usually available in 3 formats: regular over-the-counter multivitamins with 0.4 to 0.6 mg folic acid, prenatal over-the-counter multivitamins with 1.0 mg folic acid, and prescription multivitamins with 5.0 mg folic acid. (III)

### Recommendations

1. Women should be advised to maintain a healthy folate-rich diet; however, folic acid/multivitamin supplementation is needed to achieve the red blood cell folate levels associated with maximal protection against neural tube defect. (III-A)
2. All women in the reproductive age group (12–45 years of age) who have preserved fertility (a pregnancy is possible) should be advised about the benefits of folic acid in a multivitamin supplementation during medical wellness visits (birth control renewal, Pap testing, yearly gynaecological examination) whether or not a pregnancy is contemplated. Because so many pregnancies are unplanned, this applies to all women who may become pregnant. (III-A)
3. Folic acid supplementation is unlikely to mask vitamin B12 deficiency (pernicious anemia). Investigations (examination or laboratory) are not required prior to initiating folic acid

supplementation for women with a risk for primary or recurrent neural tube or other folic acid-sensitive congenital anomalies who are considering a pregnancy. It is recommended that folic acid be taken in a multivitamin including 2.6 µg/day of vitamin B12 to mitigate even theoretical concerns. (II-2A)

4. Women at HIGH RISK, for whom a folic acid dose greater than 1 mg is indicated, taking a multivitamin tablet containing folic acid, should be advised to follow the product label and not to take more than 1 daily dose of the multivitamin supplement. Additional tablets containing only folic acid should be taken to achieve the desired dose. (II-2A)
5. Women with a LOW RISK for a neural tube defect or other folic acid-sensitive congenital anomaly and a male partner with low risk require a diet of folate-rich foods and a daily oral multivitamin supplement containing 0.4 mg folic acid for at least 2 to 3 months before conception, throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues. (II-2A)
6. Women with a MODERATE RISK for a neural tube defect or other folic acid-sensitive congenital anomaly or a male partner with moderate risk require a diet of folate-rich foods and daily oral supplementation with a multivitamin containing 1.0 mg folic acid, beginning at least 3 months before conception. Women should continue this regime until 12 weeks' gestational age. (1-A) From 12 weeks' gestational age, continuing through the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues, continued daily supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid. (II-2A)
7. Women with an increased or HIGH RISK for a neural tube defect, a male partner with a personal history of neural tube defect, or history of a previous neural tube defect pregnancy in either partner require a diet of folate-rich foods and a daily oral supplement with 4.0 mg folic acid for at least 3 months before conception and until 12 weeks' gestational age. From 12 weeks' gestational age, continuing throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues, continued daily supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid. (I-A). The same dietary and supplementation regime should be followed if either partner has had a previous pregnancy with a neural tube defect. (II-2A)

## INTRODUCTION

It has been estimated that 4% to 5% of babies are born with a serious congenital anomaly<sup>1</sup>; 2% to 3% will have congenital anomalies (malformations, deformations or disruptions) that can be recognized prenatally by non-invasive ultrasound screening or anticipated through invasive diagnostic testing and 2% will have developmental or functional anomalies and minor congenital anomalies recognized at birth or during the first year of life.<sup>1</sup> Folic acid, taken orally prior to conception and during the early stages of pregnancy, plays a role in preventing neural tube defects<sup>2–25</sup> and has been associated with preventing other folic acid-sensitive congenital anomalies such as heart defects,<sup>15,26–30</sup> urinary tract anomalies,<sup>15,28,31</sup> oral facial clefts,<sup>15,32–40</sup> and limb defects.<sup>15</sup>

## FOLIC ACID SUPPLEMENTATION AND THE PREVENTION OF BIRTH DEFECTS

The initial NTD translational research study investigated folic acid supplementation for recurrence prevention of NTDs in a randomized double-blind clinical trial involving 1195 completed high risk pregnancies in women from 33 centres.<sup>2</sup> The NTD recurrence rate decreased from 3.5% in a non-supplemented group to 1% for women randomized to the group receiving an oral 4 mg folic acid supplementation daily prior to pregnancy and throughout the first 6 weeks of pregnancy.

The second NTD translational research study was a randomized controlled trial for the primary prevention of NTD occurrence.<sup>3</sup> The frequency of NTDs was zero in 2471 women receiving 0.8 mg per day of folic acid compared with 6 cases in 2391 women not receiving folic acid. This RCT study supported previous case-control studies that had provided 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.<sup>10–14</sup>

## ABBREVIATIONS

aOR	adjusted odds ratio
BMI	body mass index
CI	confidence interval
GI	gastrointestinal
MTHFR	5,10-methylenetetrahydrofolate reductase
NTD	neural tube defect
OR	odds ratio
RBC	red blood cell
RCT	randomized controlled trial

These 2 landmark RCT studies have provided the folic acid supplementation dosing evidence (from initial experimental expert opinion) for NTD primary prevention and recurrence, but they were completed in female populations without the additional exposure or benefit of folic acid food fortification that is at present in the North American food environment. These RCT folic acid dose results may need to be adjusted due to the present food environment “with folic acid fortified white flour products but more research is required for optimization of oral supplementation dose (maximum benefit; minimum or no risk) with non-pregnant pre-conception exposure to fortified food products.<sup>16</sup>

## ORAL FOLIC ACID SUPPLEMENTATION PREGNANCY CARE

Oral pre-conception folic acid dietary intake or supplementation is required as it is the primary source for the trans-placental transfer of folate/folic acid to the embryo/fetus. No specific studies have been published looking at the embryonic cell folate availability in humans during this embryonic target period of 0 to 8 weeks (conception to 10 gestational weeks). Canadian researchers have made strong contributions in this area of prevention.<sup>41–76</sup>

Women should be advised to maintain a nutritionally healthy diet, as recommended in *Eating Well with Canada's Food Guide*.<sup>42</sup> Good or excellent sources of natural folate include broccoli, spinach, peas, Brussels sprouts, corn, lentils, and oranges.

Counselling should emphasize that the recurrence risk for a fetus with an NTD is shared by both mother's and father's personal reproductive history, but only the mother is treated with the supplemental dose of pre-conception/first trimester folic acid.

## Folic Acid Food Fortification and Oral Supplementation

In Canada, since 1998, in an effort to reduce the rate of NTDs, there has been mandatory folic acid fortification of white flour, enriched pasta, and cornmeal. Food fortification coincided with an observed decrease in NTDs in live-born infants,<sup>1,6,16</sup> but a proportion of the documented NTD decrease may also be related to an increased use of prenatal tests and subsequent pregnancy termination (secondary prevention) rather than to fortification alone.<sup>45,46</sup> It is possible that certain prevalence data populations may not have included termination of pregnancy prior to the 20 weeks' gestation information in their reported rate.

Sherwood et al. assessed the dietary folate intake of pregnant and lactating women at the presently mandated and predicted folic acid fortification levels to determine the prevalence of inadequate and excessive intakes. The conclusion was, at the present mandated levels of food fortification, many pregnant and lactating women are still unlikely to meet their appropriate folate requirements from dietary sources alone, however the actual level of inadequacy cannot be determined until the level of folic acid in the food supply is known with greater precision.<sup>50</sup>

RBC folate testing/screening for the prevention of birth defects in certain co-existing maternal health conditions requires more investigation to determine the actual effectiveness and use of this testing.

### Factors that may affect the ability to achieve adequate maternal folic acid tissue levels

Optimization of oral maternal folic acid supplementation is difficult because it relies on folic acid dose, type of folate supplement, bio-availability of the folate from foods, timing of supplementation initiation, maternal metabolism/genetic factors, and many other factors.<sup>71–76</sup>

#### Recommendations

1. Women should be advised to maintain a healthy folate-rich diet; however, folic acid/multivitamin supplementation is needed to achieve the red blood cell folate levels associated with maximal protection against neural tube defect. (III-A)
2. All women in the reproductive age group (12–45 years of age) who have preserved fertility (a pregnancy is possible) should be advised about the benefits of folic acid in a multivitamin supplementation during medical wellness visits (birth control renewal, Pap testing, yearly gynaecological examination) whether or not a pregnancy is contemplated. Because so many pregnancies are unplanned this applies to all women who may become pregnant. (III-A)

## FOLIC ACID FOR CONGENITAL ANOMALIES PREVENTION AND EVALUATION

### Background for NTD Prevention

Neural tube defects are severe congenital anomalies that occur due to a lack of neural tube closure at either the upper, middle, or lower portion of the spine in the third to fourth week after conception (day 26 to day 28 post-conception).<sup>77</sup>

In Canada, the prevalence of NTDs in newborns has declined since 1998 due to food fortification and increased

vitamin supplementation,<sup>78–80</sup> as well as to an increase of prenatal diagnosis/termination.<sup>45,46</sup>

Recurrence risks may reflect the genetic contribution in different regional or population incidence and folic acid NTD sensitivity (Table 2), as there is still an estimated 1% recurrence rate even with the 4 to 5 mg folic acid prophylaxis supplementation approach.<sup>1,6,7,81–91</sup>

Table 2 summarizes the increasing NTD clinical risk groups, based on the family relationship of the affected individual to the “at-risk” fetus and the specific NTD population background risk (based on ethnic/genetic population demographics). The Canadian population risk varies across the country, with the highest NTD risk in Newfoundland and the lowest NTD risk in British Columbia.<sup>77</sup>

Table 3 summarizes the evidence-based risk factors for low maternal RBC or serum folate status that are associated specifically with neural tube defects.<sup>15,19–22,41,77–79,81,82,92–106</sup>

Table 4 summarizes the commonly used medications/drugs prescribed for certain medical therapies that have been shown to have interactions with folate metabolism and may alter RBC folate levels with a resulting increased risk for congenital anomaly outcomes.<sup>100–103</sup>

Table 5 summarizes the studies with case–control, cohort, or RCT comparisons (odds ratio) and decreased, increased, or no effects on specific congenital anomalies.<sup>15,30,37,38,40,53</sup> Folic acid in combination with multivitamin supplements has been shown to reduce certain other congenital anomalies such as heart defects,<sup>15,26–30</sup> urinary tract anomalies,<sup>15,28,31</sup> oral facial clefts,<sup>15,32–40</sup> and limb defects.<sup>15</sup> At present, multifactorial inheritance (genetic and environmental factors)<sup>79,107,108</sup> is the most commonly reported etiology for NTDs, but monogenic, chromosomal, and teratogenic etiologies have specific effects and have not been well studied in their association with folic acid deprivation or supplementation.<sup>109</sup>

The risk categories for fetal NTD outcome should consider the 2 major effect pathways:

1. Genetic factors including gene polymorphisms that affect the efficiency of folate metabolism, gene mutations, affects related to DNA methylation/epigenetics, and associated chromosomal anomalies, and
2. Environmental factors such as dietary folate intake (food fortification and/or dietary supplementation), gastrointestinal absorption efficiency, teratogenic medication exposure (epilepsy or folate antagonist medications), glucose metabolism (obesity, diabetes type I and II), drugs, smoking, alcohol, and “proposed” folate receptor auto-antibodies.

**Table 2. Anencephaly and spina bifida approximate recurrence risk with no food folic acid fortification or folate supplementation**

Relationship of NTD affected individual to the at-risk fetus	Recurrence risk, % based on population NTD incidence		
	Population incidence 5 per 1000	Population incidence 2 per 1000	Population incidence 1 per 1000
One sibling	5	2	2
Two siblings	12	10	10
One parent	4	4	4
One second-degree relative	2	1	1
One third degree relative	1	0.75	0.5

Adapted from Firth HV, Hurst JA, Hall JG. Oxford desk reference. Clinical genetics. Oxford: Oxford University Press; 2006.<sup>77</sup>

NTD: neural tube defect

**Table 3. Identified increased risk factors for fetal NTD or low maternal RBC folate status**

Personal/family history or ethnic risk <sup>1-5,19-22</sup>	NTD: maternal or paternal affected, previous affected fetus for either parent, child, sibling, or second /third degree relative MTHFR genotype 677TT carrier homozygous 677CST carrier heterozygous
Medical/surgical condition <sup>41,77-79,100-103</sup>	GI: malabsorption/inflammatory bowel, Crohn's, active Celiac disease, gastric bypass surgery, advanced liver disease Renal: kidney dialysis Pre-gestational diabetes (type I or II) Anti-epilepsy or folate-inhibiting medications (see Table 4)
Maternal co-morbidities <sup>81,92-97</sup>	Maternal obesity: BMI > 30 kg/m <sup>2</sup> or 80 kg (pre-pregnancy weight)
Maternal lifestyle factors <sup>82,98,99,190-192</sup>	Smoking Alcohol overuse Non-prescription drug use/abuse Low socio-economic status Poor/restricted diet

NTD: neural tube defect; RBC: red blood cell; MTHFR: methylenete trahydrofolate reductase; GI: gastrointestinal

**Table 4. Interactions between drugs or medications and folic acid**

1. Biology reduced folic acid activity	Interference with erythrocyte maturation	Chloramphenicol Methotrexate
	Other	Metformin
2. Reduced folic acid levels	Impaired absorption	Sulfasalazine
	Increased metabolism	Phenobarbital Phenytoin
	Not reported	Primidone Triamterene Barbiturates

**Table 5. Summary of congenital anomalies (decreased or increased or no effect) following folic acid food fortification**

Study reference	Anomaly	Case-Control (95% CI)	Cohort/RCT (95% CI)
Meta-analysis			
Goh et al. (2006) <sup>15</sup>	Neural tube defect	0.67 (0.58–0.77)	0.52 (0.39–0.69)
	Oral facial cleft	0.63 (0.54–0.73)	0.58 (0.28–1.19)
	Cardiovascular defects	0.78 (0.67–0.92)	0.61 (0.40–0.92)
	Limb reduction defects	0.48 (0.30–0.76)	0.57 (0.38–0.85)
	Cleft palate	0.76 (0.62–0.93)	0.42 (0.06–2.84)
	Urinary tract defects	0.48 (0.30–0.76)	0.68 (0.35–1.31)
	Congenital hydrocephalus	0.37 (0.24–0.56)	1.54 (0.53–4.50)
Johnson and Little (2008) <sup>38</sup>	Cleft lip and palate	0.75 (0.65–0.88)	
	Cleft palate only	0.88 (0.76–1.01)	
Single Population			
Li et al. (2013) <sup>30</sup>	<i>Heart defects isolated and complex</i>	0.52 (0.34–0.78)	
		0.27 (0.14–0.55)	
Godwin et al. (2008) <sup>40</sup>	Spina bifida	0.51 (0.36–0.73)	
	OS atrial septal defects	0.80 (0.69–0.93)	
	Ureteric obstruction	1.45 (1.24–1.70)	
	Abdominal wall defect	1.40 (1.04–1.88)	
	Pyloric stenosis	1.49 (1.18–1.89)	
Canfield et al. (2005) <sup>53</sup>	Anencephaly	0.84 (0.76–0.94)	
	Spina bifida	0.66 (0.61–0.71)	
	TGA	0.88 (0.81–0.96)	
	Cleft palate only	0.88 (0.82–0.95)	
	Pyloric stenosis	0.95 (0.90–0.99)	
	Omphalocele	0.79 (0.66–0.95)	
	Upper limb reduction	0.89 (0.80–0.99)	
O'Neill (2007) <sup>37</sup>	Cleft lip ± palate	0.61 (0.39–0.96)	Folic acid 0.4 mg daily
		0.75 (0.50–1.11)	Folate diet only
		0.36 (0.17–0.77)	Supplement + diet
	Cleft palate only	1.07 (0.56–2.03)	
Goh et al (2006) <sup>15</sup>	No effect identified for	Trisomy 21	
		Pyloric stenosis	
		Undescended testis	
		Hypospadias	

RCT: randomized control trial; OS: ostium secunda; TGA: transposition of the great arteries

Details for the genetic and environmental factors/considerations with fetal and pediatric outcomes are available in the references.<sup>19–22,110–149</sup>

### **POTENTIAL CAUTION FOR MATERNAL, FETAL, CHILDHOOD, OR GENERAL POPULATION WITH FOLIC ACID SUPPLEMENTATION**

#### **Benefit**

Folic acid, in a 0.4 to 1.0 mg daily dose<sup>60,150–152</sup> is not known to cause demonstrable harm to the developing fetus or to the pregnant woman. The risk of maternal or fetal toxicity

from oral folic acid intake due to vitamin supplements and/or fortified foods is low. Folic acid is a water soluble vitamin, so any excess intake is anticipated to be excreted in the urine.

Folic acid has not been shown to promote or to prevent breast cancer.<sup>153–155</sup>

Ovarian cancer studies 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.<sup>156</sup>



Evidence has been reported for a decreased prevalence of preeclampsia with maternal folic acid supplementation.<sup>143,157–160</sup>

An Australian study found that high serum folate did not mask the macrocytosis of cobalamin (vitamin B12) deficiency of pernicious anemia.<sup>161</sup>

A Cochrane Review found no conclusive evidence of benefit of folic acid supplementation on pregnancy outcomes (preterm birth, stillbirths, neonatal deaths, low birth weight babies, pre-delivery anemia, or low pre-delivery red cell folate).<sup>162</sup>

### Risks and Cautions

Folic acid dosing above the recommended supplementation amounts (supra-physiologic doses) has not been shown to have any added fetal/maternal health or developmental benefits, although recent epigenetic/methylation studies in animals and humans have indicated that some caution and research is required. The folic acid doses of 5 mg have not been reported to have maternal or fetal risks, but long-term high-dose 5 mg folic acid use has not been well studied in a prenatal population.<sup>3,10–14,35,36, 54,55,163</sup>

Recent summary conclusions from colorectal cancer reviews of the topic are still cautionary.<sup>164–177</sup> Two studies show no association of folic acid with colorectal adenoma or recurrence.<sup>178,179</sup>

## FETAL AND PEDIATRIC ISSUES

### Benefit

Pediatric ongoing health benefits have been identified following prenatal multivitamin supplementation before and in early pregnancy.<sup>40,128</sup> Maternal use of prenatal multivitamins is associated with a decreased risk for pediatric brain tumours (OR 0.73, 95% CI 0.60 to 0.88),<sup>40,146,180</sup> neuroblastoma (OR 0.53, 95% CI 0.42 to 0.68),<sup>40</sup> leukemia (OR 0.61, 95% CI 0.50 to 0.74),<sup>40,147</sup> Wilms' tumour,<sup>142</sup> primitive neuroectodermal tumours,<sup>145</sup> and ependymomas.<sup>145</sup> It was stated that it is not known which constituent(s) among the multivitamins confers this protective effect.

A study looking at maternal use of folic acid supplementation and the diagnosis of childhood autism found that folic acid supplementation around the time of conception was associated with lower risk of autistic disorder in a Norwegian cohort. The adjusted OR for autistic disorder in children of folic acid users was 0.61 (95% CI 0.41 to 0.90). These findings cannot establish causality but they do support the use of prenatal folic acid supplementation.<sup>148,149</sup>

### Risks and Cautions

Folic acid and multivitamin supplementation is possibly associated with an increased incidence of twins, although positive and negative twinning findings have been reported with the possible confounders of in vitro fertilization and ovarian stimulation or other environmental hormones. A clear relationship between folic acid supplementation and twinning has not been confirmed.<sup>60,181–183</sup>

A slightly increased risk of wheeze and respiratory infection was found in the offspring whose mothers took folic acid supplements during pregnancy.<sup>184</sup> It was suggested that methyl donors in the maternal diet during pregnancy may influence respiratory health in children consistent with epigenetic mechanisms. Zetstra-van der Woude et al. reported maternal high-dose folic acid (5 mg) was associated with an increased rate of asthma medication among children (recurrent asthma medication IRR [incidence rate ratio] = 1.14, 1.04 to 1.30 and recurrent inhaled corticosteroids IRR = 1.26, 1.07 to 1.47). In the cohort of 39 602 pregnancies, 2.9% were exposed to high-dose folic acid.<sup>185</sup> Associations were clustered on the mother and adjusted for maternal age, maternal asthma medication, and dispensing of benzodiazepines during pregnancy.<sup>186</sup> Veeranki et al. used a retrospective cohort of 167 333 mother–infant pairs to compare no prenatal folic acid exposure with first trimester only folic acid exposure and reported higher relative odds of bronchiolitis diagnosis (aOR 1.17, 1.11 to 1.22) and greater severity (aOR 1.16, 1.11 to 1.22). The effect was not significant in the other 2 exposed groups of “after the first trimester” or “both first trimester and after the first trimester”.<sup>186</sup>

Magdelijns et al.<sup>187</sup> and Crider<sup>188</sup> et al. did not confirm any meaningful association between folic acid supplementation during pregnancy with atopic diseases in the offspring.

More population studies are required to understand whether there is an exposure and an effect risk for pediatric outcomes, but for now some caution in favour of using the lowest effective folic acid supplementation dose is required.

### Recommendations

- Folic acid supplementation is unlikely to mask vitamin B12 deficiency (pernicious anemia). Investigations (examination or laboratory) are not required prior to initiating folic acid supplementation for women with a risk for primary or recurrent neural tube or other folic acid-sensitive congenital anomalies who are considering a pregnancy. It is recommended that folic acid be taken in a multivitamin including 2.6 ug/day of vitamin B12 to mitigate even theoretical concerns. (II-2A)

4. Women at HIGH RISK, for whom a folic acid dose greater than 1 mg is indicated, taking a multivitamin tablet containing folic acid, should be advised to follow the product label and not to take more than 1 daily dose of the multivitamin supplement. Additional tablets containing only folic acid should be taken to achieve the desired dose. (II-2A)

## COUNSELLING AND FOLIC ACID SUPPLEMENTATION

Canadian data indicates clear socio-demographic differences among women with respect to their knowledge and use of folic acid. Although most women understood the benefits of folic acid supplementation, greater than 33% did not take folic acid supplements prior to becoming pregnant and less than 50% supplemented according to national guidelines. Targeted education and other interventions to improve folic acid use in younger women and women with lower socio-economic status is recommended.<sup>189</sup>

Han et al. reported that certain groups of women (from the Caribbean, Latin America, North Africa, Middle East, China, and South Pacific) who are immigrants to Canada take fewer folic acid supplements than Canadian-born women. This immigrant group may benefit from enhanced or directed pre-conception education and counselling.<sup>66</sup>

Folic acid supplementation and the NTD risk stratified for maternal BMI requires more consideration. A recent Chinese cohort study reported the association between folic acid supplementation and the reduced NTDs risk was weaker in overweight/obese mothers (overweight/obese was defined as BMI  $\geq 24.0$  kg/m<sup>2</sup>) than in underweight/normal mothers (BMI  $< 24.0$  kg/m<sup>2</sup>).<sup>190</sup>

Oral supplementation success may be variable because of compliance issues with daily oral tablet use (nausea, “forgot,” “don’t like to take pills”) but as a result of food fortification with folic acid, Canada has almost eliminated folate deficiency.<sup>191</sup> The best predictor of prenatal multivitamin adherence in pregnant women is related to the women’s previous experiences with multivitamin use. The most important factors inhibiting prenatal vitamin use are fear or the experience of nausea, vomiting, and gagging. For women who took the supplemental vitamins, the most important factors were the dosing regimen, health care provider advice, and the mode of product distribution (prescription, over-the-counter, covered by insurance).<sup>191</sup>

The limited RCT data for folic acid supplementation in certain clinical scenarios requires the use of cohort and

case-control evaluation and expert opinion extrapolation. Alternate opinions regarding oral supplemental dosing have been published by Motherisk.<sup>192</sup>

Other long-term uses for folic acid in the other clinical use context (alcoholics, anemia, liver disease, kidney disease, malabsorption, cardiac disease, cancer treatment, regular multivitamin wellness use) are not considered or discussed in this guideline.

### Summary Statement

In Canada multivitamin tablets with folic acid are usually available in 3 formats: regular over-the-counter multivitamins with 0.4 to 0.6 mg folic acid, prenatal over-the-counter multivitamins with 1.0 mg folic acid, and prescription multivitamins with 5.0 mg folic acid. (III)

The 3 clinically at-risk groups that will benefit from folic acid supplementation are derived from evidence-based review and expert opinion, and are based on the folic acid-sensitive risk of teratogenic or genetic congenital anomaly, or the estimated risk of maternal folic acid deficiency. The supplemental folic acid requirements for the best benefit-to-risk outcome have used the published Canadian female population (post fortification) RBC folate values.

It is important to emphasize that all 3 risk recommendations for the clinically “at-risk” groups have pregnant women returning to or continuing the oral low dose 1.0 mg folic acid multivitamin supplementation at 12 weeks’ gestational age and continuing to minimize any unknown or potential risk for folic acid supplementation and the exposed mother or fetus/newborn.

**LOW risk group:** Women or their male partners with no personal or family history of health risks for folic acid-sensitive birth defects.

**MODERATE risk group:** Women with the following personal or co-morbidity scenarios (1 to 5) or their male partner with a personal scenario (1 and 2):

1. Personal positive or family history of other folate sensitive congenital anomalies (limited to specific anomalies for cardiac, limb, cleft palate, urinary tract, congenital hydrocephaly)
2. Family history of NTD in a first or second-degree relative
3. Maternal diabetes (type I or II) with secondary fetal teratogenic risk. Measurement of red blood cell folate levels could be part of the pre-conception evaluation to determine the multivitamin and folic acid supplementation dose strategy (1.0 mg with RBC folate



< 906 and 0.4 to 0.6 mg with RBC folate > 906) with a multivitamin)

4. **Teratogenic medications** with secondary fetal teratogenic effects by folate inhibition via anticonvulsant medications (carbamazepine, valproic acid, phenytoin, primidone, phenobarbital), metformin, methotrexate, sulfasalazine, triamterene, trimethoprim (as in cotrimoxazole), and cholestyramine
5. **Maternal GI malabsorption conditions** secondary to co-existing medical or surgical conditions that have been shown to result in decreased RBC folate levels (Crohn's or active Celiac disease, gastric bypass surgery, advanced liver disease, kidney dialysis, alcohol overuse)

**INCREASED/HIGH risk group:** Women or their male partners with a personal NTD history or a previous neural tube defect pregnancy

### Recommendations

5. Women with a **LOW RISK** for a neural tube defect or other folic acid-sensitive congenital anomaly and a male partner with low risk require a diet of folate-rich foods and a daily oral multivitamin supplement containing 0.4 mg folic acid for at least 2 to 3 months before conception, throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues. (II-2A)
6. Women with a **MODERATE RISK** for a neural tube defect or other folic acid-sensitive congenital anomaly or a male partner with moderate risk require a diet of folate-rich foods and daily oral supplementation with a multivitamin containing 1.0 mg folic acid, beginning at least 3 months before conception. Women should continue this regime until 12 weeks' gestational age. (1-A) From 12 weeks' gestational age, continuing through the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues, continued daily supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid. (II-2A)
7. Women with an **increased or HIGH RISK** for a neural tube defect, a male partner with a personal history of neural tube defect, or history of a previous neural tube defect pregnancy in either partner require a diet of folate-rich foods and a daily oral supplement with 4.0 mg folic acid for at least 3 months before conception and until 12 weeks' gestational age. From 12 weeks' gestational age, continuing throughout the pregnancy, and for 4 to 6 weeks postpartum or as long as breast-feeding continues, continued daily supplementation should

consist of a multivitamin with 0.4 to 1.0 mg folic acid. (I-A). The same dietary and supplementation regime should be followed if either partner has had a previous pregnancy with a neural tube defect. (II-2A)

To achieve a dose of 4.0 mg/day folic acid, women should consume a multivitamin containing 1.0 mg folic acid and add 3 single 1.0 mg folic acid tablets. (See the appendix for a summary of the risk statuses, risk groups, and appropriate folic acid dosing.)

Recognizing the challenge some clinical offices might face implementing the above recommendations based on the mode of product distribution (prescription, over-the-counter, covered by insurance) and compliance issues with taking daily multiple oral tablets,<sup>188</sup> the following simplified regimen could be considered. However, it is important to keep in mind that the folic acid intake should be at the lowest effective and safest dose.

**Low or moderate risk group:** a diet of folate-rich foods in addition to pre-conception and first trimester folic acid supplementation with an over-the-counter daily prenatal multivitamin containing 1.0 mg of folic acid.

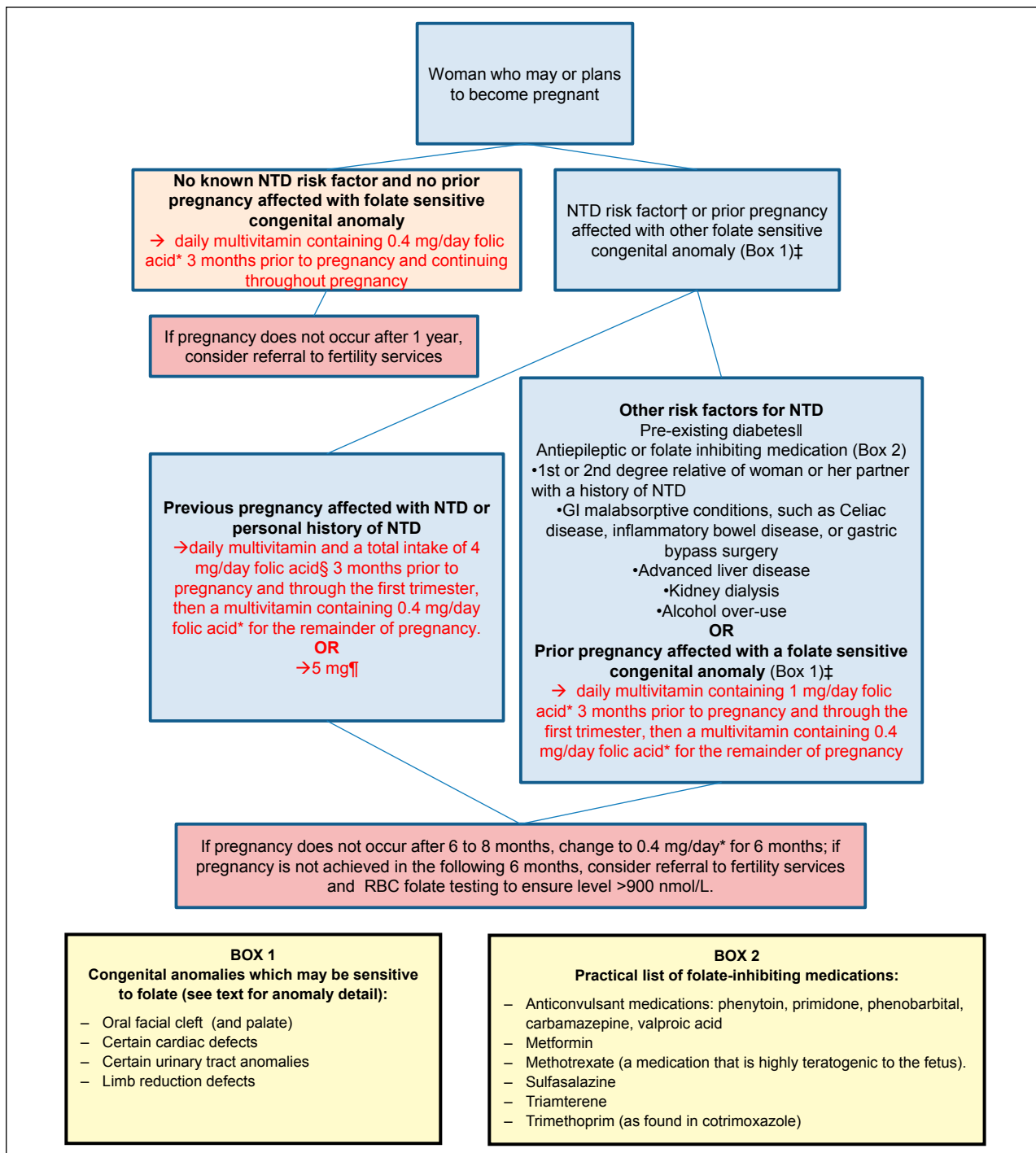
**Increased/high risk group:** a diet of folate-rich foods in addition to preconception and first trimester folic acid supplementation with a prescription daily multivitamin containing 5.0 mg of folic acid.

See the Figure for a detailed decision tree.

### SUMMARY

Folic acid (in the diet and/or as a prenatal oral supplement) with a multivitamin/micronutrient has been shown to decrease or minimize specific congenital anomalies including neural tube defects with associated hydrocephalus, oral facial clefts with or without cleft palate, congenital heart disease, urinary tract anomalies, and limb defects, as well as some pediatric cancers. The 1998 public health initiative for fortification of flour has been very beneficial with respect to primary prevention of certain folic acid-sensitive birth defects. The 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 other congenital anomalies sensitive to folic acid and multivitamins should be possible with the participation of key stakeholders. Public health surveillance strategies should be implemented to look for any adverse health outcomes (maternal; pediatric) that

Decision tree for folic acid supplementation



\*Folic acid should be taken in the form of a multivitamin containing vitamin B12. Women should not take more than one multivitamin supplement each day. In large doses, some substances in multivitamins could be harmful.

†Does NOT include spina bifida occulta as this is not a risk for NTD.

‡There are additional folate sensitive congenital anomalies that would benefit from the folic acid levels described.

§To provide a dose of 4 mg/day folic acid, a multivitamin containing 1 mg folic acid should be consumed, with single folic acid tablets added to achieve the desired folic acid dose.

||Peri-conceptual glycemic control is strongly recommended to reduce the risk of a congenital anomaly in the offspring of a woman with pre-pregnancy diabetes.

¶Folic acid intake should be at the safest and lowest effective dose; however, clinical offices that face challenges implementing recommendations for 4 mg folic acid daily because of the mode of product distribution or compliance issues with taking daily multiple oral tablets may consider the simplified regimen of one 5 mg folic acid multivitamin tablet daily.

NTD: neural tube defect; GI: gastrointestinal

could possibly be related to folic acid food fortification and additional folic acid supplementation recommendations.

## ACKNOWLEDGEMENTS

Expert opinion and guideline review were obtained from the Public Health Agency of Canada and Motherisk.

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**APPENDIX  
FOLIC ACID SUPPLEMENTATION**

Risk status	Female partner	Male partner	Folic acid dosing: A healthy folate-rich diet AND:
Low	No personal or family risk for NTD or folic acid-sensitive birth defects	No personal or family risk for NTD or folic acid-sensitive birth defects	Multivitamin with 0.4 to 1.0 mg folic acid for 2 to 3 months before conception, throughout pregnancy and for 6 weeks postpartum or to completion of lactation
Moderate	Personal history positive for folate sensitive anomalies. Family history for NTD in first- or second-degree relative. Diabetes type I or II Teratogenic medications by folate inhibition GI malabsorption that decreases RBC folate	Personal history positive for folate sensitive anomalies Family history for NTD in first- or second-degree relative	Multivitamin including 1.0 mg folic acid for at least 3 months before conception to 12 weeks and then for remainder of pregnancy and 6 weeks postpartum or to completion of lactation
High	Personal NTD history. Previous NTD pregnancy	Personal NTD history. Previous NTD pregnancy	Multivitamin including 1.0 mg folic acid plus 3 × 1.0 mg folic acid (for total of 4.0 mg) OR prescription multivitamin including 5.0 mg folic acid* at least 3 months before conception until 12 weeks' gestation, then a multivitamin including 0.4 to 1.0 mg folic acid for remainder of pregnancy and 6 weeks postpartum or to completion of lactation
*It is important to keep in mind that folic acid intake should be at the safest and lowest effective dose (4 mg/daily). However, clinical offices that face a challenge in implementing the recommended dose because of the mode of product distribution (prescription vs. over-the-counter, covered by insurance or not) and compliance issues with taking multiple oral tablets daily could consider the simplified regimen of the 5.0 mg folic acid prescription multivitamin.			
NTD: neural tube defect; GI: gastrointestinal; RBC: red blood cell			