Periconceptional intake of folic acid among low-risk women in Canada: summary of a workshop aiming to align prenatal folic acid supplement composition with current expert guidelines

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INTRODUCTION

Folate is a generic descriptor for a family of compounds that share a pteroylglutamic acid core and whose primary biological role is the transfer of 1-carbon units (1). Pteroylglutamic acid, or folic acid (FA), is the most common form of folate used in dietary supplements and as a fortificant in foods; it is completely oxidized, stable, highly bioavailable, and is seldom found in nature. In contrast, naturally occurring folates are more labile, less bioavailable, typically reduced (e.g., dihydro- or tetrahydrofolate), and frequently carry a carbon group (e.g., methyl, formyl). A significant fraction of naturally occurring folates have a polyglutamate tail which is necessary for cellular retention and affinity to various enzymes in living cells. Folate monoglutamates, but not polyglutamates, are transported across cells. Excellent sources of naturally occurring folate include green leafy vegetables, dark green vegetables (e.g., broccoli and brussel sprouts), and legumes (e.g., beans, chickpeas, lentils). Folate is best known for its role as a cofactor in nucleotide synthesis—necessary for DNA and RNA biosynthesis and repair—and for the remethylation of homocysteine to produce the essential amino acid methionine. Methionine is used for protein synthesis or can be converted to S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions in the body, including that of DNA and histones, which are required for epigenetic programming early in life (2).

Supported by the Canadian Institutes of Health Research (funding reference number 152621), to hold this 1-d workshop in Ottawa.


Received April 30, 2018. Accepted for publication July 30, 2018.

First published online December 12, 2018; doi: https://doi.org/10.1093/ajcn/nqy212.
Internationally, periconceptional supplementation with 400 μg of FA is recommended for the primary prevention of neural tube defects (NTDs), such as spina bifida and anencephaly (1, 3, 4). NTDs occur early in pregnancy, as the neural tube closes within the first 3–4 wk postconception. This recommendation is based on high-level evidence from randomized controlled trials (RCTs) and prospective cohort studies demonstrating an ≤85% reduction in NTD occurrence among women who consume FA supplements before conception and in the first trimester of pregnancy (1, 5–7). Health Canada recommends that women of childbearing age at low risk of having a fetus with an NTD consume a multivitamin supplement containing 400 μg of FA from preconception until the end of lactation (3). Health Canada requires that over-the-counter FA supplements marketed to pregnant women contain ≥400 μg FA (3). Supplements with >1000 μg FA are available by prescription only. The vast majority of prenatal supplements on the Canadian market, however, contain 1000 μg FA (8), preventing health care professionals and women from following public health recommendations. Consequently, high intakes of supplemental FA, coupled with staple food FA fortification, have resulted in very high red blood cell (RBC) folate values among pregnant women and women of reproductive age in Canada (9–12). There is no debate that folate is essential for optimal fetal growth and neural tube closure (13, 14). However, the long-term consequences of high blood folate concentrations on fetal development due to epigenetic programming or other mechanisms are unknown. Given that there is no benefit of a daily intake of FA above the recommended dose, the current FA content of prenatal supplements should be re-evaluated.

With support from a grant from the Canadian Institutes of Health Research, a 1-d workshop was held in Ottawa on 17 November 2017, with the overarching goal to align FA prenatal supplement content in Canada with evidence-based recommendations through constructive discussion among stakeholders from academia, industry, government, and health care professional bodies. The objectives of the workshop were: 1) to identify challenges and concerns from the supplement industry and health care professionals in aligning recommendations with practice in terms of FA intake of women of childbearing age and pregnant women; and 2) to identify solutions to overcome the misalignment between the recommendations and the actual FA intake.

STATE OF THE EVIDENCE

The workshop commenced with a series of presentations to provide a foundational understanding of the history of periconceptional FA supplementation, current guidelines, folate status and FA intake of Canadian women, and the benefits and potential risks associated with prenatal FA supplementation. These topics are summarized below.

Recommended dose of FA for primary prevention of NTDs

Historical perspective

FA was synthesized in the early 1940s and Lederle Laboratories manufactured 5000- and 20,000-μg FA tablets in 1945. Vitamin B-12 was identified in 1948 and was generally available for therapeutic use in the early 1950s (15, 16). Deficiencies of either of these vitamins may cause macrocytic (megaloblastic) anemia, which can be effectively treated with FA (15, 16). During the time gap between commercial availability of FA and vitamin B-12, individuals with pernicious anemia were treated with FA alone, which allowed the neurologic damage caused by vitamin B-12 deficiency to progress (1). Pernicious anemia is caused by the absence of intrinsic factor, which is secreted by parietal cells in the stomach and is required for absorption of vitamin B-12 in the small intestine (1).

In 1946, the recommended therapeutic dosages for management of folate deficiency were 5000–20,000 μg/d for adults and 5000–10,000 μg/d for children; these were not changed for 25 y (17). In 1971, the US Food and Drug Administration Drug Efficacy Study workgroup experts recommended that the Food and Drug Association lower the therapeutic dose to 250 and 1000 μg of FA for children and adults, respectively, owing to lack of evidence for greater efficacy at higher doses (18, 19).

In the 1960s, Hibbard and Smithells (20) hypothesized a link between FA and NTDs. Through a series of primarily observational studies conducted mainly in the 1970s and 1980s, it was proposed that >85% of recurrent cases of NTDs might be prevented by periconceptional FA supplementation (21). In order to establish a causal relation between FA intake and NTDs, 2 key RCTs were conducted in the 1980s and 1990s to examine the effect of FA on NTD recurrence and primary prevention (22, 23). These RCTs showed that supplemental FA in the periconceptional period (before conception and for the first trimester) significantly reduced the risk of recurrence (4000 μg FA) or primary occurrence (prenatal multivitamin containing 800 μg FA) of NTDs (22, 23). These data led to the public health recommendation that women should take an FA supplement in the periconceptional period. In Canada and the United States, these data were also used to underpin the implementation of mandatory FA fortification of white flour and other enriched cereal and pasta products (24, 25).

Recommended dose for NTD risk reduction

In the United States, it is recommended that women at high risk of having an NTD-affected pregnancy take 4000 μg FA/d, which is based on the UK Medical Research Council (MRC) Trial (Table 1) (5, 23). The MRC Trial was a randomized double-blind prevention trial to determine whether supplementation with FA around the time of conception could prevent NTDs. The dose used in the MRC Trial was selected based on observations from a small nonrandomized trial for the prevention of NTD recurrence (26). It is noteworthy that in that trial, the 4000-μg dose was chosen because that was the dose available in the hospital pharmacy at the time of the study. A dosage of 400 μg FA/d was recommended for women considered to be at low risk of an NTD, based on the knowledge that a prenatal vitamin containing 800 μg FA prevented NTD occurrence (22) and that 4000 μg FA prevented NTD recurrence (MRC), and the pragmatic reality that earlier observational studies associated multivitamins, which usually contained 360–400 μg FA, with reduced occurrence of NTDs (27, 28). In the late 1990s, a population-based public health initiative project in China was the first to show that 400 μg FA/d alone (not in the context of a multivitamin) significantly reduced the primary occurrence of NTDs (from 4.8 to 1.0/1000 in northern China and from 1.0 to 0.6/1000 in southern China) (27). The Institute of Medicine published the Dietary Reference

Table 1

<table>
<thead>
<tr>
<th>RCT</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Recurrence</th>
<th>Primary Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC</td>
<td>Randomized double-blind</td>
<td>4000 μg FA/d</td>
<td>0.025/1000</td>
<td>0.006/1000</td>
</tr>
<tr>
<td>MRC</td>
<td>Randomized double-blind</td>
<td>800 μg FA</td>
<td>0.075/1000</td>
<td>0.009/1000</td>
</tr>
<tr>
<td>NTD</td>
<td>Nonrandomized</td>
<td>400 μg FA/d</td>
<td>0.02/1000</td>
<td>0.004/1000</td>
</tr>
</tbody>
</table>
TABLE 1
Recommendations for prenatal FA supplementation in Canada and the United States

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Dose, μg</th>
<th>Definition</th>
<th>Dose, μg</th>
<th>Definition</th>
<th>Dose, μg</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>US CDC (5)</td>
<td>1991</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4000</td>
<td>Women who have had a pregnancy resulting in an infant or fetus with an NTD</td>
</tr>
<tr>
<td>US Public Health Service (29)</td>
<td>1992</td>
<td>400</td>
<td>All women of childbearing age in the United States who are capable of becoming pregnant</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Society of Obstetricians and Gynaecologists of Canada (7, 30–32)</td>
<td>1993</td>
<td>400</td>
<td>Women of childbearing age and low NTD risk planning a pregnancy</td>
<td>1000–4000</td>
<td>No NTD history, but have T1D, epilepsy treatment, first-degree relative with NTD, FA antagonist use</td>
<td>4000</td>
<td>Previous pregnancy with NTD</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>400–1000</td>
<td>Women of childbearing age and low NTD risk planning a pregnancy</td>
<td>4000–5000</td>
<td>No NTD history, but have T1D, epilepsy treatment, first-degree relative with NTD, FA antagonist use</td>
<td>4000–5000</td>
<td>Previous pregnancy with NTD</td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>400–1000</td>
<td>No personal health risks, planned pregnancy, good compliance</td>
<td>5000</td>
<td>Epilepsy, T1D, obesity with BMI &gt; 35 kg/m², family history of NTD, high-risk ethnic group (e.g., Sikh); history of poor compliance with medications, variable diet, no consistent birth control, possible teratogenic substance use (alcohol, tobacco, recreational nonprescription drugs)</td>
<td>5000</td>
<td>Previous pregnancy with NTD or other potentially folate-responsive congenital anomaly</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>400</td>
<td>Women or male partners with no personal or family history of FA-sensitive birth defects</td>
<td>1000–4000</td>
<td>First or second family history of NTD, personal history of other folate-sensitive congenital anomalies, maternal diabetes, teratogenic medications, maternal GI malabsorption conditions</td>
<td>4000</td>
<td>Personal history of NTD or previous NTD pregnancy in either partner</td>
</tr>
<tr>
<td>Health Canada and the Public Health Agency of Canada (6, 33)</td>
<td>1993</td>
<td>—</td>
<td>As early as possible, women planning a pregnancy should consult physician about FA supplements</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Previous NTD pregnancy, refer to physician</td>
</tr>
<tr>
<td></td>
<td>1995–2018</td>
<td>400³</td>
<td>All women who could become pregnant</td>
<td>Refer to health care provider</td>
<td>Refer to health care provider</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1FA, folic acid; GI, gastrointestinal; NTD, neural tube defect; T1D, type 1 diabetes.
2Women should consider a minimum of 400 μg FA or the adequate dietary equivalent according to Canada’s Food Guide to Healthy Eating.
3As part of a multivitamin containing 400 μg FA.

Intakes for folate in 1998, also recommending that women of reproductive age consume 400 μg FA/d from fortified foods or supplements (1).

Folate status, FA intake, and NTD risk

The WHO defined serum and RBC folate cutoffs for classical folate deficiency based on the relation between these biomarkers and hematologic symptoms of anemia and circulating homocysteine (28). For RBC folate, this cutoff is 340 nmol/L. The WHO also endorsed a higher RBC folate concentration cutoff of 906 nmol/L, as originally observed by Daly et al. (34), that has been associated with maximal NTD risk reduction for women of reproductive age (35, 36).

In the United States, where FA is consumed in enriched cereal grain products and ready-to-eat cereals in addition to supplements, intake modelling studies showed that women consuming enriched cereal grain products as their only source of folate had lower RBC folate status and higher predicted NTD prevalence than women consuming additional supplemental sources of FA (36, 37). Further findings have shown that achieving the optimal RBC folate concentration for NTD risk reduction requires a daily intake of ~600 μg dietary folate equivalent (~400 μg FA/d), an intake that is only achieved in women consuming FA-containing supplements in addition to fortified foods (37).

Canadian recommendations for periconceptional FA supplement use for the prevention of NTDs

Health Canada’s first recommendation for FA intake in 1993 stated that women should consult their physician about FA...
supplements as early as possible when planning a pregnancy (Table 1) (33, 38). It noted that women who have had a previous pregnancy with an NTD are at higher risk of having another NTD-affected pregnancy and should consult their physician. The guideline recommended that all women of childbearing potential follow Canada’s Food Guide to Healthy Eating and take care to choose foods higher in folate. Subsequent iterations of the Health Canada recommendation, and later also the Public Health Agency of Canada recommendation, stated that all women who could become pregnant and those who are pregnant should consume a multivitamin supplement containing 400 μg FA and women at higher risk of an NTD-affected pregnancy, such as those with a previous NTD-affected pregnancy, a family history of NTDs, diabetes, or taking an anticonvulsant drug, may require a higher dose and should refer to their physician about an appropriate FA supplement dose (6, 39–41).

The Society of Obstetricians and Gynaecologists of Canada (SOGC)’s first policy statement in 1993 on the use of FA to reduce NTDs categorized women of childbearing age as either low, intermediate, or high NTD risk (Table 1) (7). Low-risk women planning a pregnancy were recommended to consume 400 μg supplemental FA/d. High-risk women (those with a previous pregnancy affected by an NTD) were recommended to consume 4000 μg supplemental FA/d. The doses for low- and high-risk women were based on the doses used in clinical trials and observational studies. Intermediate-risk women, defined as having had no previous NTD history but being at increased risk owing to certain medical conditions or family history (Table 1), were recommended to consume 1000–4000 μg supplemental FA/d. The intermediate-risk category was based on observations that certain medical conditions are associated with higher NTD risk. Multivitamin supplements sold in Canada at the time generally contained 800 μg FA.

The SOGC guidelines for FA supplement use have since undergone 3 revisions, each of which resulted in modifications to the risk category definitions and/or the recommended doses (30–32) (Table 1). They have all recommended consuming an FA-containing supplement, in addition to consuming a healthy folate-rich diet. Importantly, in 2007, the SOGC defined low-risk women as those with no personal health risks, having a planned pregnancy, and with good compliance: the recommended dose of supplemental FA was 400–1000 μg (30). All other women were recommended to consume 5000 μg supplemental FA/d (plus dietary intake) based on an expanded list of risk characteristics including women with obesity, belonging to certain ethnic groups, with a history of poor medication compliance, and with lifestyle issues such as variable diet, inconsistent use of birth control, and possible teratogenic substance use (e.g., alcohol, tobacco, recreational nonprescription drugs). In response to confusion and concern among health care professionals about the 2007 SOGC guideline, Health Canada published a Questions and Answers for Health Professionals document to clarify the approach to identifying women that might benefit from high-dose FA supplementation (42). The current SOGC guideline, published in 2015, narrowed the 2007 risk definitions and eliminated dose ranges for risk groups (31). The daily recommended dose for the low-risk group is 400 μg FA, and the low-risk group includes women when they and their male partners have no personal or family history of an NTD or another FA-sensitive birth defect.

### Shifting folate status of Canadians

The folate status of Canadians, including women of reproductive age, has dramatically shifted over the past 50 years. The 1970–1972 Nutrition Canada Survey reported on the nutritional status of 12,795 Canadians from all 10 provinces (43, 44). At that time, 50% of Canadian women of reproductive age had serum folate concentrations that were indicative of either moderate (<12 nmol/L) or high risk (<5 nmol/L) of classical folate deficiency. A number of subsequent provincial surveys and local reports examining the folate status of women of reproductive age over the next 3 decades confirmed these biochemical findings and suggested that most women had intakes below recommendations (45–47). In 1998, the Canadian government mandated that all white-wheat flour and enriched pasta contain 150 μg FA/100 g flour and up to a maximum amount of 270 μg FA/100 g pasta, to increase the folate intakes of reproductive-aged women by 100 μg/d (24). Based on monitoring data of births and pregnancy terminations due to fetal anomalies from 7 of 10 Canadian provinces, mandatory fortification resulted in a 46% reduction in the prevalence of NTDs, from a prefortification rate of 1.58/1000 births to a rate of 0.86/1000 births postfortification (48). The first nationally representative blood folate values after FA fortification of the food supply were available from the 2007–2009 Canadian Health Measures Survey. The data indicated that classical folate deficiency as measured by an RBC folate concentration <305 nmol was virtually nonexistent (12). Among women of reproductive age, ~80% had RBC concentrations considered maximally protective against an NTD (906 nmol/L) (12).

Studies examining the sources of folate in the diet of women postfortification suggest FA-fortified foods are now major contributors to total dietary folate intake (49, 50). However, modelling nationally representative population-based data postfortification from the 2004 Canadian Community Health Survey indicated that the consumption of fortified foods alone does not result in FA intakes above the Tolerable Upper Intake Level (UL) of 1000 μg FA (51). The UL for folate refers to FA, the fully oxidized folate form, only and does not include the intake of naturally occurring dietary folate. The same modelling exercise showed that supplemental FA intakes of 325–500 μg are required by Canadian women aged 19–50 years, in addition to FA intake from fortified foods, to ensure a total intake of 400 μg of FA to meet guidance for reduction of NTDs without exceeding the UL (51).

Approximately 58% of women interviewed for the Canadian Maternity Experiences Survey reported consuming an FA-containing supplement during the 3 mo before conception (52). Whereas guidelines for low-risk women in Canada recommend a daily dose of 400 μg FA to prevent NTDs, the vast majority of pregnant women report consuming prenatal supplements containing 1000 μg of FA, as reported in 2 Canadian cohorts (50, 53). Nationally representative data on the blood folate concentrations of pregnant women in Canada do not exist. However, recent data from a demographically diverse population from Southern Ontario suggest very high maternal RBC folate concentrations during pregnancy; the geometric mean (95% CI) in early pregnancy was 2417 nmol/L (2362, 2472 nmol/L) (9). Importantly, all women had RBC folate concentrations maximally protective against NTD in early pregnancy (>906 nmol/L). Moreover, cord RBC folate concentrations were high.
Adverse effects potentially associated with high FA intake

The Institute of Medicine set the UL for FA at 1000 μg/d, based on case reports in the 1940s of precipitation or exacerbation of neurologic damage in vitamin B-12–deficient individuals (1). The UL was intended to be the usual intake level of FA at which no one would exceed the Lowest Observed Adverse Effect Level of 5000 μg.

More recently, concerns have been raised that “high” intakes of FA may have other potential adverse health consequences in addition to those related to vitamin B-12 and the UL. Systematic review of this literature is difficult owing to inconsistent application of the term “high” FA intake and/or status (54). Some potential adverse effects associated with supplemental FA intake explored in the literature include impaired fetal growth, promotion of cancer, an aggravating interaction with vitamin B-12 deficiency, and increased risk of childhood diseases such as asthma and autism. Although there exists a body of literature discussing FA and cancer (e.g., 55–60), the US National Toxicology Program and the UK Scientific Advisory Committee on Nutrition did not identify conclusive evidence on adverse effects of FA in cancer as recently reviewed (61). In the context of this workshop, however, we focused specifically on pregnancy-associated outcomes.

Studies of pregnancy- and child-related outcomes associated with prenatal supplemental FA intake for different periods in pregnancy have been summarized in Table 2. Meta-analyses and systematic reviews reported beneficial effects of periconceptional FA supplementation in addition to NTD reduction, including lower risk of small-for-gestational-age and low-birth-weight infants. The reported relations of maternal FA intake with adverse pregnancy and child outcomes are inconsistent and are solely based on observational studies and thus on lower-level evidence. Recent reviews from the United Kingdom and United States failed to identify adverse consequences of higher-dose FA on pregnancy outcomes (62). The interpretation of observational studies of supplemental FA intake is challenging owing to the biases and confounding inherent to associational studies: supplement users can be very different from nonusers in terms of important characteristics that influence health outcomes. Further, there is no agreed-upon definition of a “high” FA intake, and studies apply inconsistent cutoffs for assigning high and low groups. In addition, multivitamins represent the principal determinant of higher folate status and most often also contain vitamin B-12; animal studies can be used to propose mechanisms but their metabolism is not always directly applicable to humans. Overall, the currently available evidence on the effect of high FA intake or status is inconsistent and equivocal.

Although evidence is lacking to confirm a potential dose-dependent adverse effect of FA when supplemented across all trimesters, the “precautionary principle” could be considered in the re-evaluation or confirmation of periconceptional supplementation guidelines. The precautionary principle had its origin in environmental science and aims to anticipate, monitor, and prevent unintended adverse consequences of public health interventions. In the context of prenatal supplementation guidelines, the precautionary principle can be defined as a guide for decision making in the public health context and a policy tool for acknowledging scientific uncertainty by prompting a preventive intervention, call for more research, or both, in light of the existing state of the evidence (81).

Challenges and solutions in aligning supplemental FA intake with expert guidelines

After the formal presentations, the 38 workshop participants were assigned to 1 of 5 working groups. Equal representation in each group from each stakeholder group (i.e., academia, industry, government, and professional associations) was ensured by random assignment before the workshop. To facilitate open and frank discussion, participants were advised that although they would be identified as a workshop participant, no statement would be attributed to any individual or organization in the workshop proceedings. The working groups first convened to identify challenges in aligning FA intake for women of childbearing age with recommendations to reduce NTD-affected pregnancies in low-risk women. Once these challenges were shared with the larger group and summarized into statements, participants were asked to individually prioritize what they thought were the 5 most important challenges by placing a sticker on ≤5 of the summary statements posted around the room. The smaller working groups were then asked to reconvene to develop potential solutions to the top 5 challenges, which were then shared with the larger group. The last session consisted of a full group discussion focusing on prioritization of the solutions. The top 5 challenges and the proposed solutions are detailed in Table 3.

The challenges and solutions were interrelated and general themes emerged. First, there was a perception that the gaps in the literature on the effective FA supplement dose and duration for NTD prevention inherently resulted in different guidelines. Different guidelines have led to confusion among health care professionals and consumers. Second, a prenatal supplement containing the recommended amount of FA for low-risk women is not generally available in the marketplace, hindering health care professionals and women from adhering to the recommendations. Third, there remain barriers in Canada for some women, particularly vulnerable women, in accessing FA-containing supplements and family planning services. Fourth, there was a low level of awareness, even among workshop participants, of the harmonization of the SOGC guideline for women at low NTD risk with that of Health Canada at 400 μg FA in 2015 (31). The SOGC guideline remains a preferred resource among health care professionals, but lack of free access to the guideline constitutes a barrier to its active implementation more broadly by other stakeholders. Finally, when it comes to vitamin and mineral supplements, there seems to be a “more is better” attitude and a low level of awareness that FA intake in high

Unmetabolized FA was detectable in 97% of women, suggesting that the intake of supplemental FA exceeded the physiologic capacity to reduce and utilize FA in most women. Similarly, a recent Albertan pregnancy cohort noted an upward shift in RBC folate concentrations compared with early reports (10). However, unlike the pregnancy cohort from Southern Ontario, RBC folate concentrations were found to be below the NTD protective cutoff of <906 nmol/L in 24% of Albertan pregnant women in their first trimester (10).
<table>
<thead>
<tr>
<th>Outcomes, specific outcomes</th>
<th>Study type</th>
<th>FA dose</th>
<th>Timing of FA supplementation</th>
<th>Direction of effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW, LBW, SGA, preterm</td>
<td>Cochrane review</td>
<td>• No FA</td>
<td>• During pregnancy (studies with periconceptional FA supplementation excluded)</td>
<td>No association of FA supplementation with BW or with risk of preterm birth, stillbirths/neonatal deaths, or LBW</td>
<td>(63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA supplements (with or without other micronutrients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>Meta-analysis, systematic review</td>
<td>• No FA (15% of women)</td>
<td>• Preconceptional (25.5%)</td>
<td>Reduced risk of SGA if supplemented preconceptionally SGA &lt;10th centile (adjusted OR: 0.80; 95% CI: 0.71, 0.90; P &lt; 0.01) SGA &lt;5th centile (adjusted OR: 0.78; 95% CI: 0.66, 0.91; P &lt; 0.01)</td>
<td>(64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA taken (85%) in dosages of either: 400 μg/d (95.5%), 5000 μg/d (3.5%), or other dosage (1%)</td>
<td>• Postconceptional (74.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW (BW &lt;5th centile)</td>
<td>Meta-analysis, systematic review</td>
<td>• No FA (15% of women)</td>
<td>• Preconceptional (25.5%)</td>
<td>Preconception low-dose FA supplement: LBW adjusted OR: 0.75; 95% CI: 0.61, 0.92; P = 0.006 Postconception: not significant</td>
<td>(64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA taken (85%) in dosages of either: 400 μg/d (95.5%), 5000 μg/d (3.5%), or other dosage (1%)</td>
<td>• Postconceptional (74.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA for height, SGA for weight</td>
<td>Population-based multicenter cohort study</td>
<td>• No FA use</td>
<td>• Periconceptional (≥ 1 mo of FA use between 3-mo preconception and end of first trimester)</td>
<td>Increased risk of SGA for height for women with FA use &gt;1000 μg/d</td>
<td>(65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA use ≤1000 μg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA use &gt;1000 μg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryonic growth</td>
<td>Prospective cohort study</td>
<td>• No FA use</td>
<td>• Periconceptional</td>
<td>No or postconceptional FA use negatively associated with crown-rump-length and embryonic volume</td>
<td>(66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA use 400 μg/d</td>
<td>• Postconceptional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW, SGA</td>
<td>Prospective cohort study</td>
<td>• No FA use</td>
<td>• Periconceptional</td>
<td>Periconceptional FA intake (until end of first trimester) associated with 20% lower risk of LBW and 10% lower SGA risk</td>
<td>(67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA use 400 μg/d</td>
<td>• Preconceptional</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Postconceptional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA, LGA</td>
<td>Prospective cohort study</td>
<td>400 μg/d</td>
<td>• Periconceptional only</td>
<td>FA supplement use beyond first trimester (group of periconceptional + second + third trimester FA use) associated with increased risk of LGA compared with FA supplement in periconceptional time only; RR: 1.87; 95% CI: 1.21, 2.87</td>
<td>(68)</td>
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<td></td>
<td></td>
<td></td>
<td>• Periconceptional + second trimester</td>
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<td>• Periconceptional + third trimester</td>
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<td></td>
<td></td>
<td></td>
<td>• Periconceptional + second trimester</td>
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<tr>
<td>Childhood disease outcomes—asthma and allergic diseases</td>
<td></td>
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<tr>
<td>Asthma</td>
<td>Meta-analysis, systematic review</td>
<td>• No FA use</td>
<td>• Periconceptional or first trimester</td>
<td>No association between first trimester FA use and risk of asthma; conflicting results for second and third trimester FA use and asthma</td>
<td>(69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA use</td>
<td>• Second + third trimesters</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Any trimester/throughout pregnancy</td>
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<tr>
<td>Asthma and allergic disease</td>
<td>Review including 10 prospective cohort studies</td>
<td>Different doses</td>
<td>• Periconceptional</td>
<td>Majority of studies support no association of maternal FA intake and development of childhood asthma and allergy; limited evidence on dose-response relation between FA and risk of asthma or allergic diseases</td>
<td>(70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Preconceptional</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Postconceptional</td>
<td></td>
<td></td>
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<tr>
<td>Asthma, wheezing, dermatitis—allergic diseases</td>
<td>Prospective cohort study</td>
<td>Median (ranges) of FA: • early pregnancy 700 μg/d (43–5500 μg/d) • late pregnancy 30 μg/d (27–5895 μg/d)</td>
<td>• Early pregnancy (&lt;16 weeks of gestation)</td>
<td>FA use in late pregnancy associated with 26% increased risk of asthma at 5.5 y of age, but not at 5.5 y of age; pre- and periconceptional FA use not associated with asthma risk</td>
<td>(71)</td>
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<tr>
<td></td>
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<td></td>
<td>• Late pregnancy (30–34 weeks of gestation)</td>
<td></td>
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<tr>
<td>Wheeze, asthma, atopic dermatitis, eczema, allergic sensitization</td>
<td>Prospective cohort study</td>
<td>• No FA use</td>
<td>• Periconceptional/first trimester</td>
<td>No association between FA use during pregnancy and increased risk of developing eczema, atopic dermatitis, allergic sensitization, wheeze, or asthma</td>
<td>(72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FA use</td>
<td>• Throughout pregnancy</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Others (e.g., third trimester only)</td>
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</tr>
<tr>
<td>Childhood disease outcomes—autism/ASD/neurodevelopment</td>
<td>Systematic review (22 studies)</td>
<td>Different doses</td>
<td>• Periconceptional</td>
<td>Fifteen studies showed beneficial effect, 6 studies reported no significant findings, 1 prospective cohort study reported increased risk of delayed psychomotor development in 7- through 9-year-olds children of mothers who took &gt;5000 μg/d FA during pregnancy</td>
<td>(73)</td>
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<td></td>
<td></td>
<td></td>
<td>• Preconceptional</td>
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<td>• Postconceptional</td>
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</table>

(Continued)
TABLE 2
(Continued)

<table>
<thead>
<tr>
<th>Outcomes, specific outcomes</th>
<th>Study type</th>
<th>FA dose</th>
<th>Timing of FA supplementation</th>
<th>Direction of effect</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| ASD                         | Case-control study | • FA use (400 μg/d)  
• Multivitamin use  
• FA and/or multivitamin use (with FA 400 μg/d) |  
• Before pregnancy (i.e., 540–271 d before birth)  
• During pregnancy (i.e., 270 d before birth up to date of childbirth) | Lower risk of ASD in children of mothers exposed to FA and/or multivitamin supplements before and/or during pregnancy (adjusted RR: 0.27–0.56); no significant risk reduction in offspring of parents with psychiatric condition; no risk reduction if women took vitamin supplements before pregnancy for treatment of vitamin deficiency | (74) |
| ASD                         | Case-control study | • No FA (28% of women)  
• FA 400 μg/d (72%) |  
• Periconceptional (4 wk before to 8 wk after conception) | Reduced risk of ASD (adjusted OR: 0.61; 95% CI: 0.41, 0.90) in children (mean age 6.4 y) of mothers with periconceptional FA | (75) |
| ASD                         | Case-control study | Total FA intake summed based on data including dose, brand, frequency of supplement, and fortified food intake |  
• 3 mo before pregnancy and throughout each month of pregnancy | Lower risk (OR: 0.62; 95% CI: 0.42, 0.92) of ASD in children of women who took ≥600 μg/d compared with <600 μg/d in first month of pregnancy; decreasing OR with increasing FA intake (0, <500, 500–<800, 800–1000, >1000 μg/d) | (76) |

Childhood disease outcomes—metabolism, insulin resistance, and obesity

| Obesity/insulin resistance (HOMA-IR) | Systematic review (5 human and 9 animal studies) | In human studies/RCTs:  
• No FA use  
• FA 400 μg/d  
Folate status in observational studies | During pregnancy | Inconsistent findings; animal studies showed overall protective effect of FA on obesity + insulin resistance; human studies reported decreased risk of metabolic syndrome, and higher HOMA-IR with FA supplementation, and no or a positive association between late-pregnancy maternal folate status and HOMA-IR | (77) |

| HOMA-IR | Cluster RCT | • No FA  
• FA 400 μg/d  
• FA 400 μg/d + iron  
• FA 400 μg/d + iron + zinc  
• FA 400 μg/d in multimicronutrient supplement | Start of supplementation in early pregnancy | No association between maternal plasma folate concentration and HOMA-IR in 6- to 8-y-old children | (78) |

| HOMA-IR | Prospective cohort study | 500 μg/d | Start of supplementation at 18 weeks of gestation | Higher maternal folate status predicted higher adiposity (fat mass and body fat percentage) and insulin resistance (HOMA-IR) in 6-y-old children; highest HOMA-IR if mothers had high folate and low vitamin B-12 status | (79) |

| Body composition | Population-based birth cohort study | • No FA use  
• FA use | During pregnancy: 18 and 32 weeks of gestation | No association between maternal FA supplementation during pregnancy and body composition in 9-y-old children | (80) |

1 ASD, autism spectrum disorder; BW, birthweight; FA, folic acid; LBW, low birthweight; LGA, large-for-gestational-age; RCT, randomized controlled trial; Ref., reference; SGA, small-for-gestational-age.

Amounts may not have any added benefit and might even cause harm.

A number of research priorities and activities to facilitate the proposed solutions are described in Table 4. At a high level, solutions focused on strategies to increase awareness of the SOGC and Health Canada harmonized guidelines for FA and NTD prevention among low-risk women for both health care professionals and consumers. A refreshed public health campaign was proposed that would use innovative marketing strategies (e.g., front-of-package messaging on or coupons in sanitary products) and online social media targeting all women of childbearing age, not just those planning a pregnancy.

Based on the discussions, workshop participants felt that if health care professionals are going to advise women to take a multivitamin supplement containing 400 μg/d of FA, one will need to be made widely available. Further, ownership by all stakeholders and not deflection of responsibility will be required to move this forward. There was a general appreciation amongst workshop participants that education regarding FA recommendations for the prevention of NTDs and availability of the supplement need to occur in concert, and industry would
### TABLE 3
**Top 5 challenges and potential solutions identified by workshop participants in aligning FA intake among women with recommendations for primary prevention of NTDs**

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions and potential implementation strategies</th>
</tr>
</thead>
</table>
| Need for additional evidence on the effective dose and duration to prevent NTDs | - Commitment from professional groups to have harmonized guidelines based on the best available evidence.  
- Harmonization of definitions of women at low, moderate, and high risk of an NTD-affected pregnancy.  
- Recommendations that do not fully align with the available evidence should be acknowledged in guidelines to ensure that recommendations based on judgment are differentiated from those based on a higher level of evidence. For example, it is recommended that prenatal supplements containing FA be consumed throughout pregnancy even though FA is required for the neural tube closure in the first trimester. |
| Supplement content inconsistent with recommendations | - Education of both health care professionals and consumers on harmonized recommendations of FA to increase demand for products with the recommended dose. These efforts could benefit from the inclusion of women of childbearing age in the development of knowledge translation initiatives.  
- Reformulation should be encouraged industry-wide to mitigate risk to companies who are the first to align dose with recommendations.  
- Industry could take a stepwise approach to reformulation to allow sufficient time to transition prenatal vitamins to contain 400 μg FA.  
- Develop a multivitamin/mineral monograph specific for prenatal supplements that aligns the allowable FA content with the recommended dose of FA. Other nutrients of concern regarding pregnancy would also be included.  
- Change the maximum allowable over-the-counter dose of FA in supplements to 400 μg, resulting in doses ≥400 μg being available by prescription only.  
- Allow a label content claim on prenatal supplements indicating that the product contains the recommended dose of FA for NTD risk reduction. |

*Note: The table continues on the next page.*
### TABLE 3
(Continued)

<table>
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<tr>
<th>Themes</th>
<th>Challenges</th>
<th>Solutions and potential implementation strategies</th>
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<tbody>
<tr>
<td>Facilitating access to FA-containing supplement during periconception</td>
<td>Despite recommendations to consume an FA-containing supplement in the periconception period, many women do not consume the recommended dose (or supplements at all) because they have limited access to them. This can be due to the following:</td>
<td>- FA-containing prenatal supplements (recommended dose) and contraception should be made available to all women (e.g., free of charge to those unable to purchase). - Clinicians and policymakers should develop an increased awareness of the social determinants of health that may influence the risk of an unplanned pregnancy, the ability to access FA-containing supplements, and the ability to adhere to FA recommendations.</td>
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<tr>
<td>Knowledge transfer</td>
<td>Whereas many health care professionals are aware of the FA recommendations, many others remain unaware, resulting in lost opportunities for ensuring that women consume the recommended amount of FA. Also, many women themselves are not aware of the recommendations.</td>
<td>- More education of the public and health care professionals regarding the recommended FA intake is needed. This could be facilitated by making guidelines more widely available and engaging stakeholders, including consumers, in the development of knowledge transfer activities. - A refreshed public health campaign on FA recommendations should adopt innovative marketing strategies (e.g., front-of-package messaging or coupons on sanitary products; shelf information at the point of purchase) and online social media that target all women of childbearing age, not just those planning a pregnancy. - FA recommendations could be packaged within an overall strategy targeting women about a healthy lifestyle and family planning. - Anticipatory guidance on FA and NTD, family planning, etc., should be routinely provided to all women of childbearing age at “well woman” visits (e.g., preventive care visits; pap exams).</td>
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<td>“More is better” attitude</td>
<td>Decades ago, micronutrient deficiencies were common in Canada, and the emphasis had been on ensuring nutrient adequacy in the population. However, this “more is better” attitude persists.</td>
<td>- Messaging that “more is not always better” in terms of use of vitamin and mineral supplements could be incorporated into knowledge transfer solutions identified above. - It is important that messages should be positive without scaring women; the concept that 400 μg is sufficient should be emphasized. - Take the opportunity to have pharmacists serve as “gatekeepers” regarding the appropriate FA dose for low-risk women.</td>
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</tbody>
</table>

1FA, folic acid; NTD, neural tube defect; RBC, red blood cell; RCT, randomized controlled trial; SOGC, Society of Obstetricians and Gynaecologists of Canada.
Evidence review to address whether there would be unintended consequences of lowering the commonly consumed supplement dose from 1000 μg FA to 400 μg:
- e.g., would incidence of other folate-sensitive congenital anomalies change?
Studies of blood folate analytic methods including standard reference material to facilitate comparison across studies and populations:
- e.g., using reference material from the National Institute of Standards and Technology.
Analysis of marketing methods to better understand how to reach women before conception:
- Focus especially on those not following the FA recommendations to provide strategies to conduct targeted research projects and awareness campaigns.

Improve knowledge transfer and enhance education strategies for both health care professionals and the general public:
- Perform a scoping review of knowledge and awareness of the 2015 SOGC recommendations (identify who knows about them and what they know).
- Develop education campaigns in collaboration with pharmacist associations in Canada and support pharmacies’ ability to transfer knowledge to women by providing accurate shelf information on FA recommendations.
- Modify medical, nursing, and allied health undergraduate curricula to include the importance of the recommended supplemental FA intake before and during pregnancy.
- Integrate notions of nutrition, biology, and human health in secondary school curricula (e.g., knowledge of FA and NTDs in sex education courses).

require time to make the change. Finally, although the best available evidence in Canada suggests that 80% of women have blood values that are maximally protective against an NTD (12), very little is known about the remaining 20% in terms of who they are and whether they are capable of becoming pregnant, or have access to prenatal supplements and family planning services. An improved understanding of this group of women and how they were identified as a key research priority.

We thank Liana A Mida for contributing to workshop organization and conduct, and Stephanie Diaz-Gonzalez for her assistance on the day of the workshop. The authors’ responsibilities were as follows—all authors: contributed equally to the grant writing, development and conduct of the workshop, and manuscript writing; take responsibility for the content of the final manuscript; and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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