

# Folic acid supplementation for the prevention of neural tube defects: promotion and use

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**Abstract:** Observational and randomized controlled studies have shown that periconceptional folic acid (FA) supplementation can significantly reduce the risk of neural tube defects (NTDs). Countries across the world have adopted various strategies to increase awareness and to promote the use of FA. Nevertheless, health promotion and educational campaigns have proven to be ineffective in achieving the goal of increasing FA intake by the at-risk group. Mandatory FA fortification was a further step taken by some countries on the course toward improving folate status in the general population. Although some researchers advocate for extra folate to be added to the food supply, a number of governments have refrained from adopting the policy of mandatory fortification because of concerns raised over the potential side effects, such as cancer risk; however, epidemiological confirmation is inconsistent. After several years of the proven association between prenatal supplementation of FA and prevention of NTD, uncertainty, controversy, and indecision still hinder FA promotion and use. In this review, we summarize approaches taken by various countries and provide a framework for further steps in this area.

**Keywords:** folic acid, fortification, neural tube defect

## Introduction

The neural tube is the embryonic structure that ultimately develops into the brain and spinal cord. Development of neural tube and its closure occurs in the first 3–4 weeks of embryonic development, before a woman realizes that she is pregnant. Neural tube defects (NTDs) result from failure of the neural tube to close during early embryonic life. Failure of closure of the cranial part of the tube results in anencephaly or encephalocele, whereas failure of closure of the caudal part results in spina bifida (occult or overt), meningocele, or meningomyelocele. Incidence wise, NTDs are second to cardiac defects in list of congenital anomalies. NTDs can be isolated or can be a part of multiple malformation syndromes. The inheritance of isolated NTD follows a multifactorial pattern where the interaction between genetic and environmental factors plays a major role in the causation. Geographic, ethnic, seasonal, and socioeconomic factors play a role in determining the prevalence of NTD.<sup>1</sup> Maternal risk factors implicated in increased risk of NTD include late maternal age, diabetes mellitus,<sup>2</sup> obesity,<sup>3</sup> hyperthermia,<sup>4</sup> the use of antiepileptic drugs, such as valproic acid,<sup>5</sup> and carriage of specific genetic polymorphisms.<sup>6,7</sup>

Over the past 5 decades, there has been a rapid growth of knowledge about folic acid (FA) and its role in the prevention of NTD. The word “folate” comes from the Latin word *folium*, which means leaf. In 1931, Dr Lucy Wills showed that a yeast extract was effective in the treatment of anemia of pregnancy. In the late 1930s, folate was identified as the substance responsible for this antianemic effect. Eventually, it was isolated from spinach

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leaves in 1941.<sup>8</sup> Folate is a water-soluble vitamin found naturally in foods of animal and plant origin, especially the dark green leafy vegetables, such as spinach and cabbage. Natural folate is largely present in the polyglutamate form, which has to be converted by intestinal enzymes into active monoglutamate form for bioavailability. FA, a monoglutamate, is the synthetic form of folate used in supplements and food fortification. FA is more stable and has greater bioavailability compared with natural folate. Folate is an essential coenzyme in single-carbon transfer pathways, which are fundamental in amino acid metabolism, purine and pyrimidine nucleotide synthesis, and methylation. Hence, it is critically important for the synthesis, repair, and function of DNA and RNA. FA requirement is increased in conditions associated with an increase in the metabolic rate and rapid cell turnover, such as pregnancy. Folate requirements during pregnancy are 5–10 fold higher than those in nonpregnant women. Moreover, one-third of pregnant women are estimated to have varying degrees of FA deficiency.<sup>9</sup>

## Aims and methods

In this narrative review, we aim to describe the evolution of FA supplementation around the world at population level. We discuss the promotion campaigns, their successes, failures, and challenges in the light of new evidence regarding side effects of higher FA concentrations in general population. We have reviewed Web sites of certain countries to identify their policies, guidelines for food fortifications, and challenges faced by some reports indicating harmful effects.

## FA and NTD prevention

The mechanism by which folate supplementation reduces the occurrence of NTD is not well understood. One of the postulated mechanisms is the presence of autoantibodies that hinder the binding of folate to its receptors on the placental membranes. Consuming extra amounts of FA is postulated to overcome this blockage.<sup>10</sup> The epigenetic mechanism that impairs DNA methylation, an important step in gene expression and formation of the neural tube, is thought to have a role in the occurrence of NTD. It has been hypothesized that FA, by donating a methyl group, rectifies the biochemical process of methylation and can prevent NTD.<sup>11</sup>

In 1995, Daly et al<sup>12</sup> proposed a model that correlated maternal red cell folate levels with NTD risk in a continuous dose-response relationship. In this model, it was illustrated that NTD risk is reduced as red cell folate levels increase beyond what is considered a normal level. Periconceptional supplementation of FA has been the focus of a large number of published studies and has received a great deal of attention worldwide. This is not surprising because of the possibility of

primary prevention of a very serious congenital defect with a simple intervention. In early 1960s, Hibbard and Hibbard<sup>13</sup> reported an increased risk of NTD in a group of mothers with high incidence of folate deficiency. Numerous studies of varying design and from different parts of the world followed and arrived at the similar conclusion pioneered by Professor Richard Smithells.<sup>14–18</sup> Plausibility of the etiological role of maternal folate deficiency in development of fetal NTD was suspected.

Two landmark studies confirmed that FA supplementation protects against the recurrence and occurrence of NTD. The Medical Research Council (MRC) Vitamin Study Research Group conducted a multicenter, randomized, double-blind trial involving 33 centers in 7 countries. Women with a previously affected pregnancy with NTD were allocated to 1 of 4 supplementation groups. Those groups included supplementation with FA, other vitamins, both, or neither. The trial was terminated early after enrollment of 1,195 women by the steering committee in April 1991. The FA group had a 72% protective effect for prevention of recurrence of NTD (relative risk [RR] = 0.28; 95% confidence interval [CI], 0.12–0.71).<sup>19</sup> One year later, Czeizel and Dudas<sup>20</sup> published their work on the role of periconceptional FA supplementation in the prevention of the first occurrence of NTD in a group of Hungarian women. In a randomized controlled trial, women were randomly assigned to receive 0.8 mg of FA plus multivitamins 1 month before and 3 months after conception or a supplement of trace elements. No cases of NTD were detected in the supplemented women, whereas 6 cases were identified in the nonsupplemented women (RR = 0.07; 95% CI, 0.04–0.13). A synthesized summary of all studies reported a strong protective effect of FA against NTD.<sup>21</sup>

## Strategies to promote folate consumption

Based on these studies, various agencies and governments have issued guidelines and recommendations to promote FA supplementation for all women in the reproductive age group. The dose recommendation varies between countries ranging from 400 to 500 µg for all women of childbearing age and 4–5 mg for women who had a history of an affected child in previous pregnancy.<sup>22,23</sup> In addition to recommendations, active promotion programs were undertaken to promote use of FA on large population scale.

## National or regional health promotion programs or campaigns

Health promotion programs or campaigns to increase FA awareness and use during the prenatal period are of 2 types.

One that adopts an active outreach approach, which offers direct counseling, encourages women to take FA supplements preconceptionally, provides or pays for FA supplement and monitors the progress in the target group. Programs of this nature have shown promising results. For example, 387 young minority women were enrolled in an educational program at 3 reproductive health clinics in Texas, Huston. A trained health educator provided education on NTD, the role of FA in prevention of NTD, and the importance of taking multivitamin supplements and FA-fortified food. A 3-month supply of multivitamins was given. A follow-up survey of the program indicated that the daily intake of FA increased from 9% at the time of enrollment to 67% within 3 months into implementation of the program.<sup>24</sup> The other type of campaign takes on a more passive approach, such as a mass media campaign. This type of campaign can be effective in reaching sizable population in short time and is less costly. However, these types of campaigns lack the personal relationship with the message provider and the opportunity for follow-up and tracking progress. Moreover, it is possible that in such an approach, the majority of the audience can be of the more advantaged class of the society who have access to such media sources. It was identified in The Netherlands that 28.1% of women with low level of education and 57.5% of women with a high level of education reported hearing about FA before implementing a national mass media campaign to increase FA use. Following the campaign, though there was a significant increase in awareness in both groups, the discrepancy in awareness persisted (63.6% vs 88%, respectively).<sup>25</sup>

Many national campaigns have incorporated both approaches to reach a larger population and to achieve results that are more successful. A good example is the United Kingdom Education Authority Folic Acid Campaign that ran from 1995 to 1998. The campaign targeted women of childbearing age, health care and other professionals, and the commercial sectors. Awareness of FA supplementation increased from 51% in 1995 to 89% in 1998, and correspondingly, intake increased from 24% to 38% in women trying to conceive.<sup>26</sup> Likewise, in Western Australia, the Folate and Neural Tube Defects Prevention Project utilized a wide variety of health promotional strategies, including written material, presentations, and paid and unpaid media activities. Evaluation of the program showed that the population of women taking preconceptional FA has increased from 13% to 30%.<sup>27</sup> In China, a public health campaign was carried out between October 1993 and September 1995 in which women were advised to take a 400- $\mu$ g FA tablet daily when they came for mandatory premarital examination. Following

the campaign, the rate of NTD dropped significantly in the 2 areas surveyed, one with high (from 4.8/1,000 to 1/1,000) and the other with low rate (from 1/1,000 to 0.6/1,000) of NTD.<sup>28</sup> In Israel, where more than 90% of marriages are performed within a religious context, the national FA campaign utilized religious leaders to distribute brochures to all couples registering for marriage in addition to other strategies to promote FA consumption. Two years later, a follow-up survey reported an increase in FA intake from 5.2% to 30.5% ( $P < 0.001$ ).<sup>29</sup> We have summarized some of the health promotion campaigns carried out in various countries to promote FA awareness and use in Table 1.

## Predictors of suboptimal use of FA

Despite such successes, preconceptional use of FA has continued to be a substantial public health challenge. Fewer than 50% of women report taking preconceptional FA supplements globally (Figure 1).<sup>30,31</sup> This could be due to many reasons. Approximately 50% of all pregnancies are unplanned.<sup>32,33</sup> In addition, although increasing awareness is undoubtedly essential, it is the individual behavioral change that is ultimately required to increase compliance. A behavior change program with an effective support system, such as concrete incentives and personal follow-up, would be a better design to produce a long-term change. Changing behavior is easier said than done. Over the years, global efforts have managed to increase the awareness and knowledge of FA and its role in the causation of NTD, yet this has not translated into a significantly increased consumption of FA by the at-risk population. A significant gap between awareness, knowledge, and the actual consumption of FA appears to be universal. In the United States, a national survey showed that although 84% of women have a general awareness of FA, only 31% reported taking it daily.<sup>34</sup> Surveys in many other countries have shown a similar dissociation between the awareness and the actual use of FA.<sup>35-37</sup> Interestingly, only half of the highly motivated women, conceiving through assisted reproductive technology, took FA before conception.<sup>38</sup>

A fundamental step in constructing a health promotion campaign is the formative research where inputs and preferences of audience shape the health message delivered to enhance the anticipated behavioral change. Lindsey et al<sup>39</sup> applied this principle in studying a group of college-enrolled women between the ages of 18 and 34 years in 4 cities across the United States. The results of this study highlighted the value of incorporating the audiences' beliefs, knowledge, attitudes, and preferences in designing a health message. Furthermore, efforts spent to look at predictors of suboptimal use of preconceptional FA identified that women, who

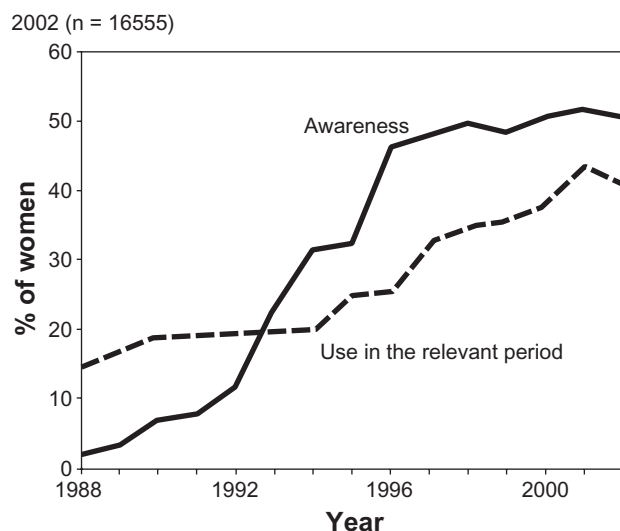
**Table 1** Description and outcome of folic acid campaigns in different countries

Program	Campaign	Outcome	Remarks
United Kingdom Health Education Authority (HEA), England (1995) <sup>26</sup>	Informative research to understand target groups (public, health professionals, and commercial sector) Educational material (leaflets, posters, advertising, media work)	Comparison to survey in 1995 (3 y after implementation) Awareness increased from 51% to 89% Use increased from 24% to 38% for women trying for a baby 49% of health professionals changed practice	Introduction of labeling scheme for folic acid – fortified food (HEA folic acid flash)
Ireland The Health Promotion Unit of the Irish Department of Health and Children (1996–2002) <sup>94</sup>	Health professionals: leaflets Public: newspapers, radio, and TV advertisements	Survey 1996 and 2002 Awareness increased from 54% to 94% Usage during pregnancy increased from 14% to 83% Periconceptual use increased from 6% to 24%	
Netherlands Government-sponsored folic acid campaign (1995) <sup>95,96</sup>	1995 mass media campaign 2004 pharmacy proactive intervention (informing and motivating women using oral contraceptives, sticker on the box of oral contraceptives, and distributing leaflets)	Comparison to survey in 1994 (4 y after implementation) Awareness increased from 27% to 73% Use of folic acid at sometime in their pregnancy increased from 7.8% to 80% Use for entire advised period increased from 0.4% to 51%	
Australia Western Australia Health Promotion Campaign (1992) <sup>27,40</sup>	Public: posters, pamphlets, seminars, presentations, paid and unpaid media activities General practitioners, pharmacists, and other health professionals: information sheets, pamphlets, posters, articles in journals, newsletters, and bulletins, presentations Promotional material distributed to child care centers, family planning facilities, public libraries, schools	Survey: 1992, N = 452 1995, N = 163 2000, N = 578 Awareness: 8.2%, 67.5%, 62.3% Usage: 1.3%, 30%, 28.5% during these respective years	General practitioners offering folic acid to women planning pregnancy increased from 9% to 70.6% 87.5% of pharmacists reported increased sale of 0.5 mg folic acid supplement
The South Australian "Folate before Pregnancy" Campaign (1994) <sup>97</sup>	Health professionals: information leaflets, pamphlets, newsletters, presentations Public: posters and pamphlets distributed in pharmacies, doctors' rooms, community health centers, health food shops, shopping centers and libraries, child care centers, preschools and high schools Information in newspapers and women's magazines, radio stations, and TV	Survey 1995, 1996, and 1998 Awareness increased from 36.7% to 52.9% to 64.1% Periconceptual usage increased from 10.1% to 26.7% to 46.1%	Pamphlets translated into 7 non-English key languages

United States CDC, March of Dimes Birth Defects Foundation and The National Council on Folic Acid (NCFA) (1999) <sup>34</sup>	Public: TV, radio, and print, public service announcements, mailing education material including brochures, posters, and postcards in Spanish and English Health professionals: educational interactive and CME web-based modules, free educational CD-ROM, training kits, reference cards, in-office educational sessions	Comparison to survey in 1995 (10 y after implementation) Awareness increased from 52% to 84% Use of daily folic acid increased from 28% to 33%	English and Spanish material
CDC and Kaiser Permanente Southern California (1998) <sup>98</sup>	Focus groups to assess factors influencing use Control group: health phone script, brochures, magazines Provider education intervention: slides, brochures, posters Direct mail/pharmacy information intervention: starter kit, video incentives, poster	Control group: usage increased from 37.5% to 41% Provider education: from 39.3% to 43% Direct mail/pharmacy information: from 35.5% to 40.3%	
Israel National Folic Acid Campaign (2000) <sup>29,99</sup>	Maternal – child health clinics: staff education, posters, patient handout in Hebrew, Arabic, and Russian Public: interviews for national radio programs, TV, magazines, newspapers, lectures, health education kit, lectures and handouts for postpartum women	Survey 2000, 2002, and 2005 Awareness increased from 54.6% to 85.2% to 90.3% Use increased from 5.2% to 30.5% to 34%	Used religious leaders to distribute brochures to all couples registering for marriage Targeted regions with high rate of fertility and NTDs Local women were trained as educators Annual folic acid awareness week
Norway National information campaigns on folate and pregnancy (1998–2000) <sup>35</sup>	Women, pharmacists, and health professionals: posters, folders, advertisements in weekly magazines, media activities, Internet Web site	Survey 1998 and 2000 Awareness increased from 50% to 60% Usage increased from 10% to 47%	
Mexico Nuevo Leon folic acid campaign (1999) <sup>100</sup>	Public: radio, TV, written press, brochures, subway tickets, posters Health professionals: seminars, conferences Free folic acid supplements to low-income families and women with previous child with NTD	9 and 28 mo after campaign Awareness increased from 44% to 51% Use increased from 32% to 44%	12,000 community volunteers and a group of medical students collaborated with the promotion

**Abbreviations:** CDC, Centers for Disease Control and Prevention; CME, continuing medical education; NTDs, neural tube defects.





**Figure 1** Trends in awareness and the use of folic acid by women. Data from a surveillance program conducted by the Slone Epidemiology Center Birth Defect Study that took place in Boston (Massachusetts, USA), Philadelphia (Pennsylvania, USA), and Toronto (Ontario, Canada). Reproduced from de Jong-van den Berg LT, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. Trends and predictors of folic acid awareness and periconceptional use in pregnant women. *Am J Obstet Gynecol*. 2005;192(1):121–128.<sup>31</sup> Copyright © 2005 with permission from Elsevier.

are young, are single, have low level of education, have less income, and are from a lower socioeconomic status, are more likely not to consume periconceptional FA.<sup>31,40,41</sup> When young (13–22 years of age) and low-income women were targeted in the FA promotion program in Huston, Texas, the daily multivitamin intake increased from 9% to 67%.<sup>24</sup> In addition, racial and ethnic disparities were found to influence FA consumption. Nonwhite and Hispanic women were the least likely to be aware of FA.<sup>34</sup> Following a paid Spanish-language media campaign in selected US states, FA awareness and usage increased significantly in the intervention group (71.1% vs 54.5% and 22% vs 15%;  $P < 0.05$ ), respectively.<sup>42</sup> Participation of physicians and other health workers is a fundamental building block of any health promotion campaign and is found to be the strongest predictor of FA use in many studies. A total of 588 women participated in a cross-sectional survey conducted at a large tertiary center hospital in Melbourne, Australia. More than half of women taking FA before pregnancy and 60% of those taking it during pregnancy said they were doing so on the recommendation of their family doctor.<sup>43</sup> Health care providers, on the other hand, are not always aware, nor do they have the time, funds, and personnel to consistently inform and stimulate women to take FA. In a random-sample telephone survey of health professionals including physicians of different specialties and practicing nurses, only 30% correctly reported the recommended dose of FA to prevent NTD recurrence.<sup>44</sup>

Nevertheless, the increased rate of FA consumption did not parallel the efforts spent to implement and establish such programs. Stockley and Lund<sup>45</sup> conducted a comprehensive review of published literature from 1989 to 2006 on the effectiveness of various interventions to improve the periconceptional use of FA. They concluded that even high-quality campaigns that result in an increase in the use of FA would have a limited impact, as more than half of the women are poorly compliant, and programs often will not reach unplanned pregnancies. Similar results were obtained from a systematic review by Chivu et al<sup>46</sup> where the average usage of FA was less than 25% following diverse interventions used to increase FA intake.<sup>45,46</sup> Furthermore, Botto et al<sup>47</sup> in a retrospective cohort study that included 8,636 cases of anencephaly or spina bifida reported by birth registries in 13 areas in Europe and Israel, identified that recommendations and broadcasting information alone did not have a measurable effect on the prevalence of NTD.<sup>45,47</sup> National integrated health promotion programs embracing information on patterns and predictors of FA consumption and incorporating public and health professional's education to implement environmental, behavioral, and social policy changes could be an effective way to develop a successful program.

## FA fortification

Another approach adopted in some countries for increasing overall FA levels at population level is food fortification. Food fortification can reach a large number of people without necessitating behavioral changes and regardless of their social, ethnic, or educational background. On the other hand, such an uncontrolled intervention exposes the entire population to FA with its potentially harmful adverse effects and long-term consequences, especially in the vulnerable group including the very young and very old individuals.

In 1998, the US Food and Drug administration led the path on the mandatory fortification trail by addition of 140  $\mu\text{g}$  of FA to 100 g of all enriched cereal grain products and flour.<sup>48</sup> Canada pursued a similar policy in the same year.<sup>49</sup> Subsequently, the policy of mandatory FA fortification was adopted in more than 40 countries across the world with varying amounts of FA added to a commonly used food vehicle consumed by the target population.<sup>50</sup> There has been a significant reduction in the incidence of NTD in countries where mandatory fortification was approved and implemented. In the United States, following mandatory fortification, a reduction of approximately 26% in the prevalence of NTD has been reported.<sup>45,47,51</sup> A similar reduction was

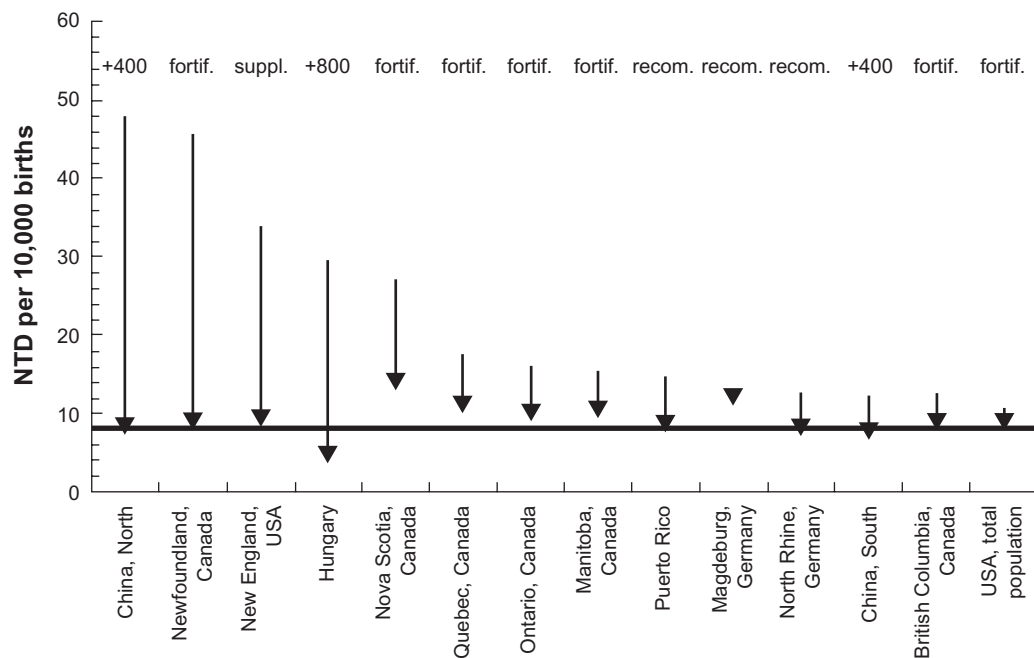
observed in Chile, where the prevalence of NTD decreased from 17.5 to 8/10,000 births.<sup>52</sup> In Canada, the prevalence of NTD decreased significantly countrywide. Overall, a 46%, 53%, and 31% reduction in the rates of spina bifida, anencephaly, and encephalocele, respectively, were observed in the postfortification period.<sup>53</sup>

Although fortification with FA served to reduce the incidence of NTD, the reduction is less than what was predicted from randomized controlled trials<sup>54</sup> (Figure 2). In Brazil, eg, mandatory FA fortification was not associated with a perceptible reduction in the prevalence of NTD, 0.72/1,000 before fortification and 0.5/1,000 after fortification ( $P = 0.16$ ).<sup>55</sup> Moreover, mandatory FA fortification did not alter the racial or ethnic difference in the prevalence of NTD.<sup>55,56</sup> In areas with low baseline rates of NTD, the benefit in the rate of occurrence of NTD was smaller compared with areas with a high baseline rate.<sup>54</sup> Possible explanations of the disappointing reduction in the rate of NTD include genetic causes of NTD that cannot be prevented by consuming excess folate and inadequate consumption of the food chosen to fortify, either because of dietary habits or because of cost and certain maternal risk factors that increase the risk of NTD occurrence and cannot be reversed by the addition of FA.

Additionally, mandatory FA fortification continued to spark debate among scientists, researchers, policy makers, and governments. Although less than 3% of adults in the

United States were found to consume more than the tolerable upper intake level of FA, ie, 1,000  $\mu\text{g}/\text{d}$ <sup>57</sup> and only around 8% of women attained the daily recommended intake of FA (400  $\mu\text{g}/\text{d}$ ) with the current fortification levels (140  $\mu\text{g}/100\text{ g}$  of enriched cereal grain), the serum folate concentration for all segments of the population in the United States more than doubled after 5 years of implementing the policy of mandatory fortification.<sup>57,58</sup> Comparable results were reported in Chile, where FA fortification was introduced in 2000.<sup>59</sup> Likewise in Canada, the mean red blood cell (RBC) folate measured in women of reproductive age (18–42 years of age) following mandatory fortification increased from 527 nmol/L to 741 nmol/L.<sup>60</sup>

Concerns were raised over the safety and potential harms of FA fortification. Exacerbation of neurological symptoms as a result of masking of vitamin B<sub>12</sub> deficiency in patients taking FA<sup>61</sup> and an increased rate of multiple pregnancies<sup>62</sup> were among the early concerns raised against fortification. Nevertheless, published results from other studies contradicted those findings.<sup>63,64</sup> The role of folate in carcinogenesis is complex. This has created a considerable challenge for governments considering mandatory fortification. Folate plays a critical role in DNA synthesis, methylation, and repair, and therefore, it contributes to the regulation of gene expression. Any interruption in these functions is thought to cause epigenetic changes that may contribute to carcinogenesis.



**Figure 2** Decline in the rates of neural tube defect in response to various methods of increasing periconceptional folic acid intake in different countries. Reproduced (with adaptation) from Hesecker HB, Mason JB, Selhub J, Rosenberg IH, Jacques PF. Not all cases of neural-tube defect can be prevented by increasing the intake of folic acid. *Br J Nutr.* 2009;102(2):173–180,<sup>54</sup> with permission from Cambridge University Press.

The relationship between folate and cancer risk has been best studied for colorectal cancer. A good body of evidence supports a protective role of folate against the development of colorectal cancer.<sup>65–68</sup> Moreover, a meta-analysis of 7 cohort and 9 case-control studies by Sanjoaquin et al<sup>69</sup> suggested a protective effect of folate against colorectal cancer. However, the results of epidemiological studies are not consistent. Recent studies raised concerns about the potential role of folate in promoting colorectal cancer. In a prospective population-based study, Van Guelpen et al<sup>70</sup> reported a bell-shaped association between plasma folate levels and colorectal cancer risk. In his study, subjects with the lowest folate levels were at lower risk of developing colorectal cancer. Furthermore, in a randomized, double-blind, and placebo-controlled clinical trial, 607 subjects with history of colorectal adenomas were allocated to either receive FA supplementation of 1 mg daily with or without aspirin or placebo and completed 6 years of follow-up. FA supplementation had no effect on overall adenoma recurrence (RR = 1.13; 95% CI, 0.93–1.37). However, the FA group had a significantly increased risk of developing advanced lesions (RR = 1.67; 95% CI, 1.00–2.80) and multiple (>3) adenomas (RR = 2.32; 95% CI, 1.23–4.35).<sup>71</sup> More recently, Wu et al<sup>72</sup> designed a double-blind randomized trial where the subjects were participants of 2 large US cohorts with history of colorectal adenoma. Participants were randomly assigned to receive 1 mg/d FA or placebo and followed for 3–6.5 years. FA supplementation was not associated with increased risk of developing at least one recurrent adenoma (RR = 0.82; 95% CI, 0.59–1.13). Folate concentrations were measured at baseline. FA supplementation was found to be associated with significant decrease in adenoma recurrence among participants with low plasma folate at baseline (RR = 0.61; 95% CI, 0.42–0.90), and no significant effect was observed in those receiving high levels of folate (RR = 1.28; 95% CI, 0.82–1.99).

Mason et al<sup>73</sup> hypothesized a temporal association between FA fortification and the increased rates of colorectal cancer in the United States and Canada, where fortification of food with FA is mandatory. The hypothesis was based on observations from nationally representative data sets from the countries that were studied. In this analysis, improved screening programs did not seem to account for the increased rates of colorectal cancer.

We have learnt from the great work done by Professor Kim and others about the dual effect of folate in cancer pathogenesis depending on the timing and dose of folate

intervention and probably the type of tissue.<sup>68,74–76</sup> In neoplastic cells, disruption of folate metabolism results in ineffective DNA synthesis and, therefore, inhibition of tumor growth. Folate supplementation, on the other hand, may promote the progression of an established carcinogenic process. Conversely, in normal tissues, folate deficiency results in impaired DNA synthesis, repair, and stability, and therefore, folate deficiency enhances, whereas modest supplementation decreases the risk of neoplastic transformation. Moreover, excessive doses of folate in the same normal tissue may enhance carcinogenesis.<sup>77</sup> Additionally, several other risk factors interact with folate in the prevention and promotion of cancer, including genetic predisposition, age, sex, alcohol, and smoking.<sup>78–81</sup>

Epidemiological studies have explored the effect of folate supplementation on the risk of other cancers. Figueiredo et al<sup>82</sup> examined the risk of prostate cancer occurrence in the randomized clinical trial by Cole et al<sup>71</sup> mentioned earlier. Although the analysis was based on a small number of cases, a factor that can result in misleading findings, the authors reported an increased risk of developing prostate cancer in the FA supplementation group. On the other hand, higher concentration of FA was not associated with pancreatic cancer.<sup>83–85</sup> Oaks et al<sup>86</sup> even reported decreased risk of pancreatic cancer in women. Similar contradictory findings on the effect of folate supplementation on the risk of breast cancer have been reported from the literature.<sup>87,88</sup>

Another unresolved question is the effect of folate supplementation on the risk of cardiovascular disease. Folate is a coenzyme in the regulation of homocysteine metabolism and has a homocysteine-lowering effect. Hyperhomocysteinemia is associated with a greater risk of cardiovascular disease.<sup>89,90</sup> FA fortification can be considered for lowering the homocysteine levels to positively influence cardiovascular disease risk.<sup>91</sup> In contradiction, Bazzano et al<sup>92</sup> performed a meta-analysis of 12 randomized controlled trials comparing FA supplementation in persons with history of vascular disease with either placebo or routine care and found FA was ineffective in the secondary prevention of cardiovascular diseases in the population studied.

The implication of folate status in improving or worsening various medical conditions was summarized by Lucock and Yates.<sup>93</sup> In this review, some studies showed a beneficial effect in preventing some congenital anomalies (urinary tract and cardiovascular defects), fetal growth restriction, recurrent pregnancy loss, and Alzheimer disease. On the other hand, others demonstrated a negative effect on insulin resistance in



pregnant women and rheumatoid arthritis. Yet, many studies are still surrounded with uncertainty.

## Implications for practice and future directions

Prevalence studies showed a decrease in the rates of NTD even before the implementation of mandatory FA fortification. Whether this phenomenon was related to better nutrition, increased awareness, and use of folate supplements or improved prenatal diagnosis and termination of affected fetuses remains unclear. Mandatory fortification did manage to reduce the incidence of NTD, but again we cannot rule out the attribution of the above-mentioned factors to the reduction observed. A practice that improves folate status in the periconceptional period is faced with crucial dilemmas including the best way of delivering it, determining the minimum effective dose for prevention of NTD, and how to correlate serum or RBC folate with the desired outcome. The multifactorial inheritance complicates the picture further, as there will still be cases that are not responsive to FA. Campaigns conducted to increase awareness and use have proven to be only marginally effective. However, public health campaigns are still needed in countries that chose the “do no harms” over the “do good” strategy. In addition, one could argue that both health promotion programs and mandatory fortification work in conjunction to confer optimal protection against NTD. Certain key features of a potentially successful program are highlighted in Table 2. Defining the audience, reaching the population of women who are less likely to comply, ensuring funding to sustain the effort, free of cost distribution, and learning from previous

**Table 2** Key elements of a potentially successful campaign

Understanding the target population: age, geographical region, language spoken, race/ethnicity
Incorporating and making use of the audiences' input, thoughts, preferences, knowledge, beliefs, and interaction with environment to formulate and deliver a health message suitable for the target group
Targeting young women with a low level of education, lower socioeconomic status, and lower income
Utilization of various ways of delivering a health message: media, marketing, and education
Educating and training health care providers
Preconceptional health counseling by all health care providers: general practitioners, pediatricians, obstetricians and gynecologists, physician assistants, nurses, and pharmacists
Reinforcing and following up on a health education message (sustaining educational efforts)
Evaluating and tracking changes, progress, and health impact

successful programs are all measures to enhance the success rate. Feedback from the target population is a valuable line in drawing a picture of the health message.

## Implications for research

The mechanism of action of folate in reducing the incidence of NTD should be a priority research area. Research efforts should be directed toward understanding the genetic and metabolic basis of NTD and the protective role of FA. This will also allow us to understand actual requirements of FA without leading to side effects. The controversy surrounding addition of folate to food consumed by the general population and the impact of fortification on the prevention or promotion of the carcinogenic process, cardiovascular disease, and other chronic conditions should be looked at and addressed in larger surveillance studies. Prevalence studies and registries around the world play a fundamental role in evaluating the epidemiology of NTD. Clear definition of the condition, outlining the purpose of the surveillance program, using multiple sources for ascertainment, and including all cases of stillbirths and terminations are substantial in determining rates and trends of NTD and evaluating the effect of various measures taken to alter its epidemiology. Not only that but also worldwide application of a unified system to monitor NTD will serve to better compare the effect of different strategies employed to prevent a congenital defect with wide geographic, seasonal, ethnic, and racial variations.

## Acknowledgment

Mother-Infant Care Research Center is supported by funds from Ministry of Health and Long-term Care, Ontario, Canada.

## Disclosure

The authors report no conflicts of interest in this work.

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