

Review

# Folic acid—the scientific debate as a base for public health policy

M.C. Cornel <sup>a,\*</sup>, D.J. de Smit <sup>b</sup>, L.T.W. de Jong-van den Berg <sup>c</sup>

<sup>a</sup> *Clinical Genetics and Human Genetics, VU University Medical Center, EMGO B57, D423, P.O. Box 7057, 1007 MB, Amsterdam, The Netherlands*

<sup>b</sup> *I&K Com, Abcoude, The Netherlands*

<sup>c</sup> *Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute of Drug Exploration, Groningen, The Netherlands*

Received 28 February 2005; received in revised form 27 March 2005; accepted 29 March 2005

## Abstract

Randomized controlled trials have proven that periconceptional folic acid intake reduces the risk of neural tube defects (NTDs). This lead to different public health policies: fortification of foods in many countries and supplementation in some others. We concentrate here on pro's and con's of fortification policies. Meanwhile, new beneficial but also potential adverse effects are being hypothesized. Highest level evidence is available for the protective effect of folic acid on NTDs. Lower level evidence suggests other protective effects, but also some potential adverse effects, such as masking Vitamin B-12 deficiency, increasing twinning rates and an 'acceleration phenomenon' in pre-existing malignant neoplasms. While observational studies show lower cancer rates associated with increased folate intake, some case reports and animal experiments suggest opposite effects. Thus, public health policy makers are facing the question of balancing beneficial and potential adverse effects repeatedly. We propose that the scientific debate no longer focuses on NTDs alone, but that a comprehensive evaluation be undertaken by a public health authority with experience in complex meta-analyses and technology assessment.

© 2005 Elsevier Inc. All rights reserved.

**Keywords:** Folic acid; Public health; Neural tube defects; Fortification; Supplementation; Prevention; Adverse effects

## Contents

1. Introduction .....	411
2. Concerns regarding adverse effects .....	412
2.1. Masking Vitamin B-12 deficiency .....	412
2.2. Spontaneous abortion .....	412
2.3. Multiple births .....	412
2.4. Cancers .....	413
3. Comments .....	413
References .....	414

## 1. Introduction

More than 10 years ago, it became clear that folic acid substantially decreased the risk of neural tube defects (NTDs) [1,2]. Public health authorities in many countries have taken

steps to improve the periconceptional intake of folic acid in women planning pregnancy or women at risk of getting pregnant [3–7]. Soon after the publication of the MRC trial, the US government decided to move forward to fortification of staple foods. Canada, Mexico, Chile, Hungary and several developing countries followed and are now fortifying staple foods or have decided to do so in the near future [6,7]. In the early 1990s, a protective effect of folic acid against

\* Corresponding author. Tel.: +31 20 4440051; fax: +31 20 4444181.  
E-mail address: [mc.cornel@vumc.nl](mailto:mc.cornel@vumc.nl) (M.C. Cornel).

cardiovascular diseases later in life was suspected already [8]. A protection against a birth defect that occurs in some 1 in 1000 births was thus expected to be of greater significance, not only for women of childbearing age to prevent birth defects, but both for men and women later in life for a potential protective effect against cardiovascular disease. Since the start of fortification, research moved on and several studies found protective effects for many other congenital anomalies [9] as well as other diseases [10–13]. Few of these were studied in randomised controlled trials, and most evidence stems from observational studies.

Public health policies developed in two ways: some American and developing countries choose to fortify staple foods [6,7], while most western European countries so far have decided not to do so, Hungary and Ireland being the only exceptions. In many of the Western European countries, fortification is nevertheless allowed, and some specific products are available, fortified breakfast cereals being an example of such a specific product that is available in many European countries.

Seven European countries had official health education initiatives to promote the use of folic acid supplements. Despite the measures taken to date, the majority of women in all countries surveyed are not taking folic acid supplements periconceptionally. This is reflected in the lack of a clear decline in the prevalence of NTDs across Europe [5].

The effectiveness of folic acid fortification in improving folic acid status has already been shown with a dramatic increase in blood measurements of folate and a significant reduction (approx. 15–50%) in the prevalence of NTDs in the United States, Canada and Western Australia [14–16]. Improving folate status in the general population may provide other health benefits in addition to the NTD rates. Many epidemiological studies attempt to elucidate the long-term effects of folic acid fortification on anaemia, cardiovascular disease, hypertension, other congenital defects such as heart anomalies and clefts, neuropsychiatric disorders and cancers [7,10–13]. Despite the observed beneficial effects of folic acid fortification on folate status and prevalence of NTDs there continues to be some concern about folic acid fortification. While new potential beneficial effects are being studied, also potential dangers are mentioned. One of the reasons for the inertia on folic acid fortification is the fear for adverse effects. We will now briefly discuss suspected adverse effects in historical order.

## 2. Concerns regarding adverse effects

### 2.1. Masking Vitamin B-12 deficiency

Although folate is safe and almost free of toxicity, there is concern that folic acid (the synthetic form) may mask symptoms of Vitamin B-12 deficiency, primarily in the elderly population, and may lead to progression of neurological symptoms. Vitamin B-12 deficiency has been estimated to

affect up to 10–15% of the population over 60 years of age [17]. Because of this, the amount of fortification chosen was estimated to be 140 µg per 100 g flour (US), providing on average 100 µg additional folic acid/day. In this way, only a very small proportion of the population will receive >1 mg/day. The upper limit of 1 mg was chosen by the Institute of Medicine as unlikely to produce masking. Some argue that intakes below 1 mg/day may also cause masking. Because of the potential of masking the diagnosis of Vitamin B-12 deficiency, several European countries decided not to adopt mandatory food fortification. This delay in folic acid fortification in some European countries was characterised by an American author as “public health malpractice” [6]. Vitamin B-12 deficiency has not become more severe in the USA after more than 1 billion person-years of exposure to multivitamins [6]. Furthermore, should Vitamin B-12 deficiency be a frequently occurring problem, then this could be easily corrected by increasing its intake, either by simultaneous fortification or as medication in patients with pernicious anaemia.

### 2.2. Spontaneous abortion

Published reports on the relation between folic acid supplementation during pregnancy and risk for miscarriage have been inconsistent. Several studies have reported that folic acid deficiency and defects in folic acid metabolism are associated with an increased risk for pregnancy loss [18]. By contrast, analyses of data of the two randomized trials [1,2] found first of all a 16% increase (significant) in miscarriages among women in the Hungarian trial who consumed a multivitamin with 800 µg folic acid compared with women with only trace elements and furthermore a 15% non-significant increase among women in the MRC trial who received 4000 µg folic acid [19]. The hypothesis these authors mentioned was that folic acid may influence the viability of fetuses with malformations. A large population-based cohort study with 23,806 births and 2155 miscarriages of first pregnancies in China found no evidence that daily intake of folic acid influenced their risk for miscarriages [20]. Neither did a case-control study on the relation between plasma folate levels and the risk of spontaneous abortion. In this study, low plasma folate levels were related to a higher risk of miscarriages [21].

### 2.3. Multiple births

Five studies have suggested the possibility of an increase in the occurrence of multiple births [22–26]. In the randomized controlled trial (RCT) of Czeizel [22] as well as in the retrospective study of Werler [23], the increased prevalence of multiple births among folic acid users was not significant. Moreover, these studies did not differentiate among types of vitamin supplements. In the RCT, a multivitamin preparation with 800 µg folic acid was used. Two studies with Swedish data described the increased occurrence of dizygotic twins [24,25]. A total of 6953 Swedish women reported the use

of folic acid in early pregnancy among 576,873 women who gave birth during this period. Maternal age, parity, smoking, previous spontaneous abortions and involuntary childlessness appeared to act as confounders. After exclusion of women who reported involuntary childlessness and women who used ovarian stimulation, and adjusting for year of birth, maternal age, parity and smoking, the odds ratio for dizygotic twinning was 1.71 (95% CI 1.21–2.42). As only a very small proportion of women used folic acid, this group might differ in other respects, and further study is needed here. Another recent study in Hungary showed an adjusted OR of 1.80 (95% CI 1.14–2.85) [26]. If the occurrence of multiple births were caused by folic acid, the effect might be expected to be greater with increasing folic acid dose. This was, however, not observed [27]. In a large population-based prospective cohort study among young women in China with 242,015 births and 1496 multiple births, no increase of multiple births (nor of dizygotic twins) was found in women who had taken folic acid supplements compared with those who did not. This study was performed among young women and only 400 µg folic acid pills were consumed [28]. Although the available evidence is not conclusive, the large study from China which includes many young mothers and where the use of ovarian stimulation is not common, did not show an increased risk of twinning after periconceptual folic acid use.

#### 2.4. Cancers

Although folate appears to be preventive in the development of new cancers in persons without pre-existing premalignant lesions or neoplastic foci, there are also signals that folate may enhance the development and progression of already existing, undiagnosed premalignant and malignant lesions [29,30]. An ‘acceleration phenomenon’ in pre-existing malignant neoplasms was reported decades ago in children with acute leukaemia, who received a supra-physiological dose of folic acid [30]. Antifolate treatment (methotrexate) was less effective in children with acute lymphoblastic leukaemia who received more physiological doses of folic acid [30]. Finally experiments in mice suggest that folate may as well protect against cancer or have an opposite effect, however, there is a paucity of high-quality data [30].

In patients with already existing, undiagnosed premalignant and malignant lesions, low folate status is expected to disrupt DNA synthesis and replication, via reduction of purine and thymidine synthesis, and to inhibit tumor growth [29]. This has indeed been the basis of the use of folate antagonists in cancer treatments. Moreover, folate is involved in DNA methylation, an epigenetic phenomenon that is able to regulate gene expression, maintenance of DNA integrity and stability, chromosomal modifications and the development of mutations. Carcinogenesis is associated with global hypomethylation, but hypermethylation of specific genes, e.g. tumor suppressor genes, may also be involved in the etiology of cancer [31]. According to Kim, it is, therefore,

possible that in addition to folate deficiency, a high folate status can have detrimental effects on DNA and cancer risk [29]. Whether or not folic acid promotes the progression of cancer, long-term follow-up studies are warranted to determine the effect of folic acid on the incidence of cancer and on DNA methylation and other epigenetic regulatory machinery especially in countries that have adopted mandatory generalized folic acid fortification. In this regard, a recent Canadian study showing that folic acid fortification was associated with a significant reduction in the incidence of neuroblastoma among children aged <18 year is an important piece of information in this discussion [32] and in line with previous epidemiological studies which showed a protective effect of perinatal folic acid use against the incidence of brain tumors in offspring [29].

### 3. Comments

Whether or not to fortify foods with folic acid is a decision that is often discussed in the context of neural tube occurrence only or mainly. From a scientific point of view, this may be wise, since the evidence for the protecting effect of folates on NTD birth prevalence is the best type of evidence possible. However, from a public health point of view, one needs to bear in mind that the impact of a higher folic acid intake might affect the frequency of many other disorders as well. Apart from protective effects, adverse effects need to be taken into account.

Policy making in public health often implies balancing of pro’s and con’s [7]. As an example of the pro’s in several organ systems, Oakley estimated that globally, 500,000 children are born each year with spina bifida and anencephaly, two of the most common and severe birth defects [6]. “Increased consumption of supplemental, synthetic folic acid by fortification of staple foods will prevent approximately 375,000 of these birth defects each year. In the USA, this lead to a feeling of urgency, as after the advent of the polio vaccine, because ‘in little time’ the implementation of fortification programs will ‘do so much’”. Further preventive effects on the mortality from stroke and heart attacks, and the disappearing of folate deficiency anaemia added to the feeling that a ‘miracle’ had happened. As a result of fortification, in the USA, some 800 annual cases of spina bifida and anencephaly and some 22,000 annual heart attack deaths and 5000 stroke deaths had been prevented, according to Oakley [6]. The dosage of folic acid in the USA was rather low, and fortification in some countries, especially in some of the participants in the Pan American Health Organization, was chosen to be higher, potentially leading to even more prevention.

Also some of the potential adverse effects have been discussed in a context of several disease outcomes. Wright et al. [30] calculated that for one NTD case prevented, many elderly people with undiagnosed pernicious anaemia would be exposed to >1 mg/day folic acid. They also discuss the uncertainties of a decreasing incidence of cancer as compared to a negative impact on pre-existing malignant neoplasm’s.

Pro's related to NTD's need to be balanced against all other potential risks and benefits. The strategy chosen to implement fortification could vary: one of the alternatives is to fortify with folic acid and Vitamin B-12, thus tackling the problem of Vitamin B-12 deficiency simultaneously [30]. Some argue that "we consider it essential that the mechanisms by which folate modulates malignant neoplasm's be elucidated, and fully understood, before a mandatory mass 'whole population' folic acid fortification policy is enacted" [30]. However, half of London would have suffered from cholera for decades if the observation that water supplied by one company caused much more cholera than did water from another company had not lead to public health action, long before the vibrio cholera had been recognized. In this case, no balancing of pro's and con's for public health was involved, but also many drugs are being used long before their working mechanism is fully understood. For drugs, the likelihood of curing one disease usually needs to be balanced against the risk of (know or unknown) side effects. When admitting fortified products on the market, the advantages for some need to be balanced against the potential disadvantages for others. This needs to be made more explicit in political and societal debate.

From a normative point of view, it is obvious that public health authorities should do good and follow the beneficence principle, but the difficulty for policy makers is that they have to balance the certainty of benefits to an as yet unknown amount of risk to harm. Thus the maleficence principle leads to reticence to move forward. The precautionary principle thus leads to two opposite consequences: avoiding potential harm of a fortification or supplementation as initiated by governments, but also avoiding that many people ingest adequate amounts of folic acid, that many children are born healthy and many elderly have reduced risks of cardiovascular disease and cancer. The debate is even more complex, as for some of the impact on public health there is best level evidence, and for some other impacts, we have to rely on a lower level of evidence.

A third ethical principle besides beneficence and maleficence, namely autonomy, also needs to be discussed in this context. A government policy to fortify implies a decision taken for an entire population, without asking for individual decision making and informed consent. Obviously, political decision making in a transparent manner as well as information to the public at large can be guaranteed, but public health decisions demand a different ethical balancing of pro's and con's than individual health care. In order to maximize social utility, preventive strategies need to be chosen that are very effective and efficient. Whether or not informed decision making is possible depends mainly on the strategy of implementation. If many flour products are fortified, and some are not, then labelling of products will allow consumers to make their own choices. Prohibiting food fortification does not contribute to autonomy anyway.

For any public health decision on fortification with folic acid (and Vitamin B-12) to be taken, we suggest that all available evidence is taken into account. For those potential effects

(either protective or adverse) where evidence is lacking, studies need to be performed to get the answers as soon as possible, for instance the proportion of the elderly that need additional Vitamin B-12, the strategy to identify and treat deficiencies at an early stage, the balance between the number of cases of cancer avoided and the impact on pre-existing malignant lesions. Registrations and monitoring systems may help to study the frequencies of birth defects, twinning, cancer and cardiovascular disease and thus to evaluate the impact of preventive interventions. A public health authority that has experience in public health decision making based on scientific evidence, including meta-analysis and technology assessment, should undertake such a comprehensive evaluation. Reticence to fortify should be replaced by a pro-active attitude to collect the evidence needed for adequate policy making, so that both the health of future generations can be promoted and fears for adverse effects can be addressed adequately.

## References

- [1] MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet* 1991;338:131–7.
- [2] Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327:1832–5.
- [3] Cornel MC, Erickson JD. Comparison of national policies on periconceptional use of folic acid to prevent spina bifida and anencephaly (SBA). *Teratology* 1997;55:134–7.
- [4] Botto LD, Lisi A, Robert-Gnansia E, et al. International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? *BMJ* 2005, doi:10.1136/bmj.38336.664352.82. Feb 18 [Epub ahead of print].
- [5] EUROCAT Folic Acid Working Group. Prevention of neural tube defects by periconceptional folic acid supplementation in Europe, 2003, <http://www.eurocat.ulst.ac.uk/pdf/PartI.pdf>.
- [6] Oakley GP. Inertia on folic acid fortification: public health malpractice. *Teratology* 2002;66:44–54.
- [7] Oakley GP, Johnston RB. Balancing benefits and harms in public health prevention programmes mandated by governments. *BMJ* 2004;329:41–3.
- [8] Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995;274:1049–57.
- [9] Botto LD, Olney RS, Erickson JD. Vitamin supplements and the risk for congenital anomalies other than neural tube defects. *Am J Med Genet C Semin Med Genet* 2004;125:12–21.
- [10] Lucock M. Is folic acid the ultimate functional food component for disease prevention? *BMJ* 2004;328:211–4.
- [11] Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ* 2002;325:1202.
- [12] Reynolds EH. Folic acid, ageing, depression, and dementia. *BMJ* 2002;324:1512–5.
- [13] Forman JP, Rimm EB, Stampfer MJ, Curhan GC. Folate intake and the risk of incident hypertension among US women. *JAMA* 2005;293:320–9.
- [14] Honein MA, Paulozzi LJ, Mathews TJ, Ericson JD, Wong LY. Impact of folic acid fortification on the US food supply on the occurrence of neural tube defects. *JAMA* 2001;285:2981–6.

- [15] Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ* 2002;167:241–5.
- [16] Bower C, Ryan A, Rudy E, Miller M. Trends in neural tube defects in Western Australia. *Aust N Z J Public Health* 2002;26:150–1.
- [17] Institute of Medicine. Folate. Dietary reference intakes for thiamin, riboflavin, niacin, Vitamin B6, folate, Vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 196–305.
- [18] Ray JG, Laskin CA. Folic acid and homocysteine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: a systematic review. *Placenta* 1999;20:519–29.
- [19] Hook EB, Czeizel AE. Can terathanasia explain the protective effect of folic-acid supplementation on birth defects? *Lancet* 1997;350:513–35.
- [20] Gindler J, Li Z, Zheng J, Correa A, Sun X, Wong L, et al. Folic acid supplements during pregnancy and risk of miscarriage. *Lancet* 2001;358:796–800.
- [21] George L, Mills JL, Johansson AL, Nordmark A, Olander B, Granath F, et al. Plasma folate levels and risk of spontaneous abortion. *JAMA* 2002;288:1867–73.
- [22] Czeizel AE, Metneki J, Dudas I. The higher rate of multiple births after periconceptional multivitamin supplementation: an analysis of causes. *Acta Genet Med Gemellol (Roma)* 1994;43:175–84.
- [23] Werler MM, Cragan JD, Wasserman CR, Shaw GM, Erickson JD, Mitchell AA. Multivitamin supplementation and multiple births. *Am J Med Genet* 1997;71:93–6.
- [24] Ericson A, Kallen B, Aberg A. Use of multivitamins and folic acid in early pregnancy and multiple births in Sweden. *Twin Res* 2001;4:63–6.
- [25] Kallen B. Use of folic acid supplementation and risk for dizygotic twinning. *Early Hum Dev* 2004;80:143–51.
- [26] Czeizel AE, Vargha P. Periconceptional folic acid/multivitamin supplementation and twin pregnancy. *Am J Obstet Gynecol* 2004;191:790–4.
- [27] Mathews P, Murphy M, Wald NJ, Hackshaw A. Twinning and folic acid use. *Lancet* 1999;353:191–2.
- [28] Li Z, Gindler J, Wang H, Berry RJ, Li S, Correa A, et al. Folic acid supplements during early pregnancy and likelihood of multiple births: a population-based cohort study. *Lancet* 2003;361:380–4.
- [29] Kim YI. Will mandatory folic acid fortification prevent or promote cancer? *Am J Clin Nutr* 2004;80:1123–8.
- [30] Wright AJA, Finglas PM, Southon S. Proposed mandatory fortification of the UK diet with folic acid: have potential risks been underestimated? *Trends Food Sci Technol* 2001;12:313–21.
- [31] Verma M, Srivastava S. Epigenetics in cancer: implications for early detection and prevention. *Lancet Oncol* 2002;3:755–63.
- [32] French AE, Grant R, Weitzman S. Folic acid food fortification is associated with a decline in neuroblastoma. *Clin Pharmacol Ther* 2003;74:288–94.