Folic Acid Fortification: Current Knowledge and Future Priorities

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Background.

"Folate" is a generic term for compounds that have a common vitamin activity, including compounds that are naturally present in foods as well as the synthetic form, folic acid (FA), which is used in supplements and for food fortification. Metabolically, natural folates and FA are converted to coenzyme forms required in numerous one-carbon transfer reactions involved in the synthesis, inter-conversion and modification of nucleotides (purine and thymidine), aminoacids (methionine from homocysteine) and other essential structural and regulatory compounds (1).

Food sources of folate are green leafy vegetables, citrus fruit and juices, whole grain bread and legumes. These folate forms are very labile, resulting in a significant loss of biochemical activity during harvesting, storage, processing and preparation, over periods of days or weeks; this is in contrast to the stability of FA, the fully oxidized monoglutamyl form which is almost completely stable for even years. FA is more stable in foods and exhibits greater bioavailability than natural folates. As a consequence, the low bioavailability (25-50%) and poor chemical stability of the natural folates determine a rather poor supply of folate from the diet in contrast with the significant amounts supplied by fortified foods. This concept has a practical application in defining dietary folate equivalents (DFE), which is used to convert all forms of dietary folate and folic acid from fortified foods to equivalent amounts (1).

Until the 1990's, recommended intakes of folate were based on the prevention of anemia, especially during pregnancy, a state seen in the most severe phase of folate deficiency. Since then evidence has shown that low folate intake, not sufficient to cause anemia, is associated with important negative effects on health. Today, these low folate intakes are common in people consuming a limited and unvaried diet all over the world, however, very scarce data on different populations folate status exists. Evidence shows that when folate intake increases there are important health benefits. The main scientifically demonstrated benefit is that the majority of neural tube defects (NTDs) can be prevented by the periconceptional ingestion of FA, representing the first congenital malformations to be preventable through public health measures such as supplementation and /or food fortification (2,3).

Evidence of Effectiveness of FA Fortification

Recent publications from US and Canada and Chile showed that mandatory FA fortification of cereal products are associated with a significant increase in population folate status and also with significant reductions in NTD prevalence.

a) USA. Folic acid fortification of grain products and ready -to- eat- breakfast-cereals has clearly increased folate status in the United States. A comparison of pre-fortification data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) with the 1999 NHANES (post-fortification) indicated an almost threefold increase in the mean serum folate concentration in women aged 15-44 y after the initiation of fortification (4). The increase appears to be associated with consumption of folic acid in fortified foods because the data for supplement users were evaluated separately. Honein et al (5), using US birth certificates from 45 states, mandatory for all live-births, showed a total decline in NTD rate of 19% from the pre-fortification period (October 1995- December 1996) to post-fortification period (October 1998- December 1999). Williams et al (6) used data from 24 US population-based birth defects surveillance programs, including prenatally diagnosed NTD and electively terminated cases, to demonstrate a 26% total decline in NTD rates when comparing before (January 1995 to December 1996) and after (October 1998 to December 1999) mandatory fortification.

b) Canada. The effect of mandatory food fortification was evaluated in women of 18-42 years from January 1, 1996 to December 31, 1997 (pre-fortification) and January 1, 1998 to December 31, 2000 (post-fortification). Red blood cell folate increased significantly (7). Reductions of 50% and 54% in NTD rates were reported from studies done in Ontario (8) and in Nova Scotia (9) respectively. In Ontario, the Canadian Congenital Anomaly Surveillance System was used to estimate the incidence of live births and stillbirths between 1986 and 1999 and hospital data was used for therapeutic abortions. In Nova Scotia, using a population-based retrospective study design, the incidence of NTD in live-births, stillbirths and terminated pregnancies, was evaluated during a 10 year period (1991-2000). Data for NTD in live-births and stillbirths was obtained from the Nova Scotia Atlee Perinatal Database, which was abstracted from hospital records, and data for terminated pregnancies was obtained from the Fetal Anomaly Database. Another Canadian report from Ontario (10) reported a 42% reduction in the prevalence of neural tube defects after fortification.

c) Chile. In Chile, mean intake of bread is very high and consumption is widespread. Bread represents 90% of total consumption of wheat flour, which has been fortified with iron (as ferrous sulfate) B1, B2 and niacin since the 50`s. Starting January 2000, the Chilean Ministry of Health legislated to add 2.2mg FA per kg wheat flour to reduce the risk of Neural Tube Defects (NTD). This policy resulted in an estimated mean additional supply of FA of 427 g/d and significant increases in serum and red cell folate in women of reproductive age one year after fortification (11).

The frequency of NTD (anencephaly, encephalocele and spina bifida) was studied in all births, both live and stillbirths, with birth weight > 500 g in the nine public maternity hospitals of Santiago, Chile during 1999-2000 (pre-fortification period) and 2001-2002 (post-fortification period) in a prospective hospital-based design. During the pre-fortification period (1999-2000) there were a total of 120,566 newborns and the NTD rate was 17.1 /10,000 births. During the post-fortification period (2001-2002) there were a total of 117,704 newborns and the NTD rate was significantly reduced by 43 % to 9.7/10,000 births (RR= 0.57, 95% IC= 0.45-0.72) (12). This effect was observed in a dramatically short period of time and was temporally associated with folic acid fortification of wheat flour.

Current Research

a. Cost-Effectiveness of FA fortification: Chile

The presence of neural tube defects is associated with permanent neurological deficits that affect the survival and functional status of children born with this birth defect. The economic burden of spina bifida reflects the cost of providing direct medical care, rehabilitation care, developmental services, and special education as well as the indirect cost derived from the cost for families of affected individuals and their loss of productivity. Therefore, a program that reduces the incidence of neural tube defects could produce substantial societal benefits. In an ongoing evaluation of the economic gains resulting from the program we have estimated the cost of one year of folic acid fortification and the cost averted from preventing spina bifida. For the mill industry, one year of flour fortification costs approximately US$ 280,000; this cost only includes the addition of folic acid to the existing premix added to flour and conducting analytical testing for folic acid content. A before and after evaluation of the program estimated that about 50% of women of reproductive age reached the target intake of 400 ug/day, thus, we expected that approximately 1,800,000 out of 3,600,000 women in childbearing years obtained the benefits of folic acid fortification, making the cost per woman US$ 0.16. The cost of surgery and rehabilitation per child with spina bifida was shown to be approximately US$ 100,000. When applying this cost to the 110 cases of spina bifida prevented by the folic acid fortification program, total savings for the health care system may approach US$11,000,000. In comparison with the estimated cost of folic acid fortification, these economic gains appear overwhelming (13).

b. Results of ongoing trials of FA effects on vascular diseases.

Fortification has reduced the prevalence of neural tube defects, nevertheless a major unresolved question is whether increased intake of folic acid will reduce the overall incidence, morbidity and mortality of vascular disease. Data from controlled intervention trials like those supporting the role of folic acid in NTD risk reduction are not available. Recent data from Finland (Kuopio Study) (14) and from the Centers for Disease Control and Prevention, (15) support the view that increased folate intake could have a positive effect on our health. Data from other sources, including the Vitamin Intervention for Stroke Prevention trial (VISP) (16) and the Homocysteine Studies Collaboration (17) do not confirm this finding. Preliminary data from the CDC suggest that folic acid fortification has had a striking effect on mortality, particularly on stroke mortality. These data could be reflecting the effect of fortification with low-dose folic acid vs. the high-dose multivitamin combinations used in the VISP trial and in most other ongoing trials? Today evidence is conflicting so we need to wait for the results from large-scale ongoing clinical trials.

Practical Issues:

a. Low priority for FA fortification in many countries

Folate deficiency at the population level is not recognized as a public health priority in the majority of developing countries due mainly to the fact that prevalence data is scarce. Moreover, NTDs are often not recognized as important causes of morbidity and mortality as long as health conditions do not improve sufficiently to make birth defects stand out as important causes of infant mortality.

b. **Limited information on consumption of food vehicles for fortification by target population.**

Generally only data on per capita consumption of foods that could potentially be used as fortification vehicles are available. In order to estimate the potential increase in intake resulting from fortification, it is essential to obtain data on the consumption distribution of these foods by different population groups according to socioeconomic status, urban-rural dwelling, age and sex.

Future Priorities and Recommendations

Increase priority for FA (and B-12) fortification by:

1. Further research on benefits of FA fortification including reduction in other congenital malformations (cleft palate, cardiovascular malformations) and effects on vascular diseases.
2. Conduct research on the prevalence of B-12 deficiency and the health outcomes related to B-12 fortification to expand the scientific basis for B-12 fortification.
3. Expand rationale for FA fortification beyond NTD prevention, for example, by redefining folate deficiency. Currently, there are some constraints with respect to the definition of folate deficiency at the population level, especially in developing countries. First, most of the folate status studies are based only on plasma folate determinations. Second, there is a recognized variability of analytical methodology to measure blood folate, resulting in higher folate levels when radio assays versus microbial assays are employed. Third, current cut-off levels were set based on microbial assays, and they are usually applied to results obtained with any other technique. It seems important that cut-off levels be revised.
4. Advocate for benefits of FA and B-12 fortification.
5. Expand research on consumption of food vehicles for FA fortification by target populations.
6. Develop and test low-cost methodologies to measure FA content of premix samples and fortified wheat flour.

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