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Folate fortification: enough already?[1,2]

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The Food and Drug Administration mandated the folate fortification of grain products in the United States by January 1998. The primary driving force behind this policy was the recognition that periconceptional folate supplementation in addition to normal dietary folate intake significantly reduced the incidence of neural tube defects (NTDs), one of the most common birth defects (1, 2). Food fortification rather than supplementation in planning pregnancies was deemed necessary because of a perceived failure of public health efforts to influence those persons most at risk and because the neural tube closes during the fourth week of gestation, a time when many women are unaware of their pregnancy. Because of concerns that folate fortification may mask symptoms of vitamin B-12 deficiency, primarily in the elderly population, the level of fortification chosen was estimated to provide on average 100 μg additional folic acid daily with only a very small proportion of the population receiving > 1 mg. The upper limit of 1 mg was a round number chosen by the Institute of Medicine (IOM) (3) as unlikely to produce masking, although the folate intake that produces masking is controversial, with some arguing that intakes < 1 mg may cause this effect.

Many postfortification studies that assessed food composition and dietary intakes have suggested that the increased folate intake in the US population may be about twice that originally anticipated (4, 5). The article by Quinlivan and Gregory (6) in this issue of the Journal reinforces this suggestion. They used data from studies in which the effects of various folic acid intakes on plasma folate concentrations were analyzed to show a linear relation between the increase in plasma folate and folic acid intake. These authors then extrapolated data from 2 published studies on the rise in fasting plasma folate in populations not taking supplements after fortification (7, 8) to predict the additional folic acid intake in these populations. They concluded that the average additional intake of folic acid after fortification is ≈220 μg/d, which suggests that a higher proportion of the US population than anticipated may have total folate intakes > 1 mg, even in the absence of folate supplements.

The IOM based the current recommended dietary intake of folate for adults on a series of studies in which graded levels of folic acid were used (3). Because folic acid is believed to be more bioavailable than is food folate, they used a factor of 1.7 for converting folic acid to food folate equivalents. An additional 220 μg folic acid in the diet would be equivalent to ≈380 μg food folate, an amount similar to the recommended dietary allowance (RDA) for adults. Although this conversion factor is somewhat controversial (and confusing), if it had not been applied, the RDAs would have been set at an equivalently lower level so that the effect of fortification would still be an average increase in folate intake equivalent to the RDA. Of course, this increase is additional to the folate that is naturally present in the diet.

Despite this more than doubling of the folate intake in the US population, the debate continues about whether more folate should be added to the food supply. Those concerned with birth defects point out that the IOM suggests that women who are of childbearing age and capable of becoming pregnant should take a supplement of 400 μg folic acid/d in addition to their normal dietary intake to reduce their risk of NTDs (3). Other studies also concluded that the maximum benefit may be obtained by supplementing the diet with 400 μg folic acid/d (9). Proponents also point to the potential benefits of additional folate in reducing cancer risk and homocysteine concentrations, a risk marker for vascular disease. However, the elegant studies of the Framingham cohort by the Tufts group have shown that fortification in nonsupplement takers has reduced the incidence of abnormally low plasma folate from 21% to < 2%, whereas the incidence of mild hyperhomocysteinemia dropped from 21% to 10% after fortification (7). Of note, the main attributable factor responsible for elevated homocysteine has switched from folate status to vitamin B-12 status. Additional folate in the food supply is unlikely to significantly further influence homocysteine concentrations, and epidemiologic studies on cancer risk suggest that the risk is associated primarily with low dietary folate intakes (10).

The most extensive study on the effects of folic acid fortification reported a 19% drop in the rate of NTDs in the United States (11). Because ≈30% of the population takes vitamin supplements and presumably would not be expected to derive significant benefit from fortification, the actual effect may be closer to a 30% decrease, if due to fortification. However, NTD rates in the United States (and worldwide) were decreasing before fortification began, possibly as a result of factors such as improved nutrition or prenatal diagnosis and termination. Thus, it is not possible to definitively attribute the decrease in the incidence of NTDs in the United States solely to fortification. In a study in China, folic acid supplements reduced the incidence of NTDs from 4.8 to 1.0 per 1000 live births (80%) in a high-incidence region and from 1.1 to 0.6 per 1000 live births (40%) in a region with a lower incidence (12). In the US study, the incidence of NTDs was lower, ≈0.4 per 1000 live births. Because not all NTDs are folate responsive, it may be

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that the maximum benefit of fortification has already been achieved—we just do not know.

The reason why folate influences NTD rates is not known. NTDs are a low-penetrance condition influenced by environmental factors such as folate intake and genetic factors such as polymorphisms in folate genes. It is not known whether the population at risk of NTDs is all or just a small subset of pregnant women. Because the possibility exists that additional fortification may reduce the risk of NTDs further, what is the harm? Over the past few years, the US population has been exposed to a significant increase in folate intake for which there are essentially no data on safety. Practically no studies have been done to look directly or even indirectly for the adverse effects of elevated folate intakes. Although the potential masking effect of folate on vitamin B-12 deficiency is not a traditional measure of toxicity, it is a very serious concern from a public health viewpoint because of the high prevalence of vitamin B-12 malabsorption in the elderly (3). Folate supplements have not been available in megadose formulations because of this concern, so no opportunity for serendipitous discovery of any adverse effects of high intakes, as was seen for some other water-soluble vitamins, has been available.

A recent study showed the fetal loss of adverse polymorphic genotypes in folate genes (13). One could speculate that elevated intakes might protect against fetal loss because of adverse genotypes and could potentially result in increased folate requirements. One recognizes that NTDs can be a lifelong debilitating condition. However, prudence suggests that the effects of a greatly increased folate intake on the ≈270 million persons in the United States without NTDs should be evaluated before even more folate is added to the food supply. Many clinical intervention trials are currently studying the effect of folate supplements on indicators of vascular disease and disease incidence. It is hoped that these studies will also assess the safety aspects of elevated folate intakes.

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